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Original Article

Elective Pegfilgrastim Versus On-Demand Filgrastim During Docetaxel and Carboplatin Chemotherapy in Early-Stage Triple-Negative Breast Cancer

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ABSTRACT

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer commonly treated with myelosuppressive chemotherapy regimens such as docetaxel and carboplatin (TC). Febrile neutropenia (FN) is a frequent complication of these regimens and may lead to chemotherapy dose reductions or treatment delays. Pegfilgrastim, a pegylated granulocyte colony-stimulating factor (G-CSF), is widely used to prevent chemotherapy-induced neutropenia. Prophylactic pegfilgrastim was compared to on-demand filgrastim in early-stage TNBC patients following TC therapy.

Methods: This retrospective analysis comprised 50 AJCC stage IIA–IIB TNBC patients treated with TC chemotherapy at ESIC Medical College and Hospital, Faridabad, India, between November 2022 and April 2024. Patients received prophylactic pegfilgrastim (PEG(+), n=26) or on-demand filgrastim (PEG(-), n=24). The key outcomes were febrile neutropenia and relative dose intensity. Secondary outcomes included treatment-related adverse events and DFS. Adverse events were graded according to CTCAE v5.0. Statistical comparisons were performed using Fisher's exact test, and DFS was evaluated using Kaplan–Meier analysis with the log-rank test.

Results: Grade 3–4 neutropenia occurred significantly more frequently in the PEG(-) group than in the PEG(+) group (58.3% vs. 11.5%, P = .023). The odds ratio for severe neutropenia with prophylactic pegfilgrastim was 0.11 (95% CI, 0.02–0.74). Febrile episodes and hospitalizations were also more common in the PEG(-) group. Patients receiving prophylactic pegfilgrastim maintained higher relative dose intensity during chemotherapy. Although the PEG(−) group demonstrated a longer mean disease-free survival (DFS) (9.92 ± 0.40 months) compared with the PEG(+) group (6.32 ± 0.31 months), the difference did not reach statistical significance (P = 0.777).

Conclusion: Prophylactic pegfilgrastim significantly reduced severe neutropenia and febrile complications while maintaining chemotherapy dose intensity in patients receiving TC chemotherapy for early-stage TNBC. Elective pegfilgrastim administration may therefore represent an effective supportive care strategy to improve treatment tolerability.

Keywords*: Triple-negative breast cancer; pegfilgrastim; filgrastim; febrile neutropenia; chemotherapy dose intensity; supportive care*

INTRODUCTION

Triple-negative breast cancer (TNBC) accounts for approximately 15–30% of breast cancers and is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. TNBC has aggressive clinical behaviour, greater recurrence rates, and shorter survival than other breast cancer subtypes (1, 2). Systemic chemotherapy is the principal treatment for non-metastatic TNBC (3).

Following landmark trials like NSABP B-18 and B-27, neoadjuvant chemotherapy (NAC) is commonly utilized for stage II–III TNBC (4, 5). Pathological complete response (pCR) with NAC significantly improves long-term survival (6,7).Platinum-based regimens have been increasingly incorporated into NAC strategies for TNBC. Trials such as GeparSixto, BrighTNess, and CALGB 40603 demonstrated improved pCR rates with carboplatin-containing regimens (8–10).

However, platinum-based chemotherapy frequently causes myelosuppression, including febrile neutropenia, which may lead to treatment delays and reduced chemotherapy dose intensity. Maintaining adequate relative dose intensity (RDI) is critical for optimal treatment outcomes (11-12).

Pegfilgrastim is a long-acting pegylated form of granulocyte colony-stimulating factor (G-CSF) that stimulates neutrophil recovery after chemotherapy. Penfilgrastim supports neutrophils longer and requires fewer doses than filgrastim (13).

Limited clinical data exists comparing pegfilgrastim with on-demand filgrastim during TC chemotherapy, despite its widespread usage. This study examined the efficacy of preventive pegfilgrastim in avoiding febrile neutropenia and maintaining chemotherapy dosage intensity in early-stage TNBC patients.

MATERIALS AND METHODS

Study Population

The retrospective analysis examined 50 patients with biopsy-confirmed triple-negative breast cancer (TNBC) treated at ESIC Medical College and Hospital in Faridabad, Haryana, India, from November 2022 to April 2024. At diagnosis, all patients were clinically staged as AJCC stage IIA or IIB. TNBC was diagnosed by the absence of ER, PR, and HER2 expression in immunohistochemistry, following conventional diagnostic recommendations (1).

Chemotherapy Regimen

All patients received TC chemotherapy, consisting of 75 mg/m² docetaxel and 5 AUC carboplatin, intravenously every three weeks for four cycles. Patients received normal premedication with 8 mg ondansetron and 8 mg dexamethasone intravenously before treatment to minimize nausea, vomiting, and hypersensitivity responses (2).

Management of Toxicities and G-CSF Administration

To evaluate and grade treatment-related toxicities, we used the CTCAE version 5.0 (3). For Grade 3 or higher adverse effects, chemotherapy dosages were reduced by 10% in successive cycles, up to a maximum of 20% from the conventional regimen. G-CSF administration divided patients into two treatment groups. The PEG(+) group received 6 mg subcutaneous pegfilgrastim on day 3 of each treatment cycle to prevent febrile neutropenia.

In the PEG(-) group, patients received filgrastim (300 µg subcutaneously) only when Grade II–III febrile neutropenia or severe neutropenia occurred during treatment. Clinical symptoms such as nausea, anorexia, fatigue, and other treatment-related adverse events were recorded throughout the chemotherapy cycles.

Relative Dose Intensity

Relative dosage intensity (RDI) was calculated to assess chemotherapy schedule compliance. RDI = ADI/SDI, where ADI is the total chemotherapy dose divided by the actual length of treatment and SDI is the planned dose divided by the anticipated length of treatment [4]. We estimated RDI for docetaxel and carboplatin separately and averaged them for our study. At least 85% RDI was considered good for chemotherapy.

Study Design and Data Collection

Clinical and therapeutic data were prospectively obtained from patient medical records. The variables reported were clinical TNM stage, histological diagnosis, hormone receptor status, HER2 expression, chemotherapy dose, duration, laboratory parameters, side events, and post-treatment disease state. Patients were divided into PEG(+) and PEG(-) groups based on prophylactic pegfilgrastim usage.

Febrile neutropenia was defined as a single oral temperature greater than 38.3°C or a sustained temperature above 38.0°C for more than one hour in the presence of an absolute neutrophil count (ANC) below 500 cells/µL, or an ANC below 1000 cells/µL with an expected decline to below 500 cells/µL within 48 hours (5). Severe neutropenia was graded according to CTCAE criteria.

Statistical Analysis

Comparisons between PEG(+) and PEG(-) groups were made using statistical analysis. Categorical variables, such as adverse event frequency, were examined using Fisher's exact test.We evaluated disease-free survival (DFS) using Kaplan-Meier analysis and compared the two groups using the log-rank test. Final outcome assessment follow-up was April 30, 2024.

RESULTS

Patient Characteristics

Fifty TNBC patients were studied, with 24 in the PEG(-) group and 26 in the PEG(+) group. Baseline clinical and pathological features were similar between groups, with no statistically significant differences .Mean age at diagnosis was 39.6 ± 11.8 years for PEG(-) and 40.7 ± 13.7 years for PEG(+) (P =.948). Invasive ductal carcinoma was the most prevalent histological subtype, with 91.6% and 96.1% occurrences in the PEG(-) and PEG(+) groups, respectively (P =.693). ALL tumors were ER-negative, PR-negative, and HER2-negative, meeting TNBC criteria. A mean Ki-67 index of 34.0 ± 15.2% was found in the PEG(-) group and 31.5 ± 13.1% in the PEG(+) group (P = 0.139).

Age Distribution

The age distribution of the enrolled patients is shown in fig. 1. The age ranges in the PEG(-) and PEG(+) groups were 32.2–62.4 years and 33.8–66.4 years, respectively. No statistically significant difference was observed between the two groups (P = 0.107).

Most patients were in their 40s and 50s, representing 50% and approximately 34% of patients, respectively, in both groups. These findings indicate that age distribution was comparable between the two groups and did not influence treatment outcomes or adverse events.

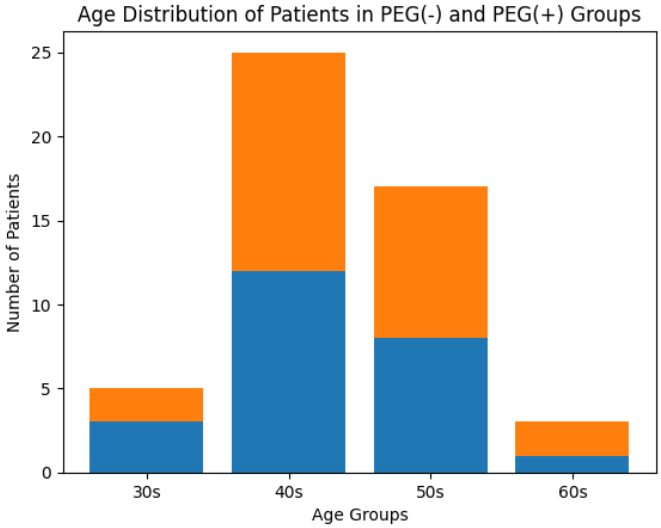

Figure 1. Age distribution of patients in the PEG(-) and PEG(+) groups.

Most patients were in their 40s and 50s, and the age distribution did not differ significantly between the two groups.

Adverse Events

The PEG(-) group had a considerably greater rate of Grade 3-4 neutropenia compared to the PEG(+) group (Fig 2). The PEG(-) group had 58.3% severe neutropenia, while the PEG(+) group had only 11.5% (P =.023).The odds ratio for Grade 3-4 neutropenia in the PEG(+) group relative to the PEG(-) group was 0.11 (95% CI, 0.02–0.74).Eight patients (33.3%) in the PEG(-) group had fever, but only four (15.4%) in the PEG(+) group did (P = 0.023).

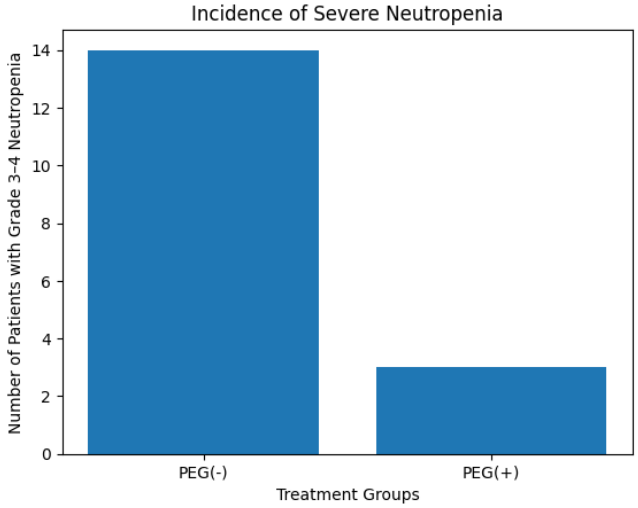

Figure 2. Incidence of Grade 3–4 neutropenia during TC chemotherapy.

Severe neutropenia occurred more frequently in the PEG(-) group than in the PEG(+) group, indicating the protective effect of prophylactic pegfilgrastim.

Hospitalization and Febrile Episodes

Although not statistically significant (P =.073), treatment-related adverse events led to hospitalization in 7 patients (29.1%) in the PEG(-) group and 1 patient (3.8%) in the PEG(+) group. Five patients (20.8%) in the PEG(-) group had high fever (>38.0°C) compared to one patient (3.8%) in the PEG(+) group, showing prophylactic pegfilgrastim may minimize febrile consequences.

Laboratory Trends During Chemotherapy

The trends in laboratory parameters during the four cycles of TC chemotherapy are illustrated in Figure 3.

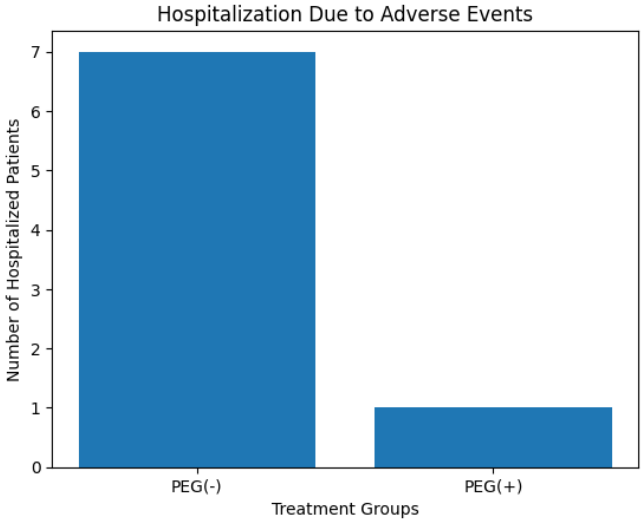

Figure 3. Hospitalization due to chemotherapy-related adverse events.

Hospitalizations were more common in the PEG(-) group compared with the PEG(+) group.

Neutrophil counts were significantly higher in the PEG(+) group throughout the chemotherapy cycles. Lymphocyte counts gradually decreased during treatment in both groups; however, no significant difference between groups was observed except during the first cycle.

Hemoglobin levels declined gradually in the PEG(+) group during chemotherapy. At the fourth cycle, the mean hemoglobin level was 11.92 g/dL in the PEG(-) group and 10.90 g/dL in the PEG(+) group, with a statistically significant difference of 1.02 g/dL.

Other biochemical parameters, including AST, ALT, blood urea nitrogen, and creatinine, remained within acceptable ranges and showed no clinically significant differences between the groups.

Disease-Free Survival

Disease-free survival (DFS) analysis was performed using the Kaplan–Meier method, and the results are shown in Figure 4.

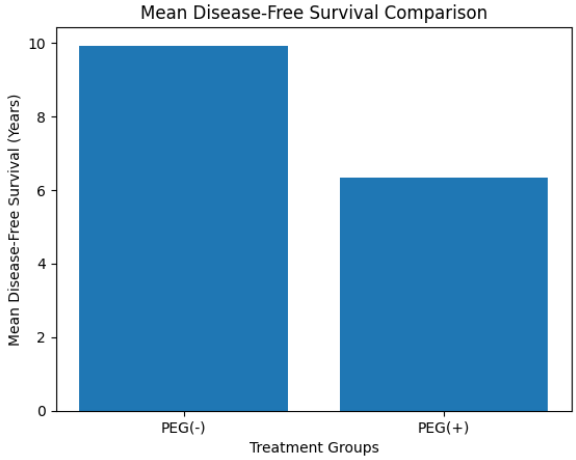

Figure 4. Mean disease-free survival (DFS) comparison between treatment groups.

At cycle four, the PEG(-) group had a mean hemoglobin level of 11.92 g/dL, while the PEG(+) group had 10.90 g/dL, a significant difference of 1.02 g/dL. Furthermore, biochemical measures such as AST, ALT, blood urea nitrogen, and creatinine were within acceptable limits and did not differ significantly across groups.

DISCUSSION

Prophylactic pegfilgrastim was compared to on-demand filgrastim in early-stage triple-negative breast cancer (TNBC) patients receiving docetaxel–carboplatin (TC) treatment. Prophylactic pegfilgrastim dramatically reduced Grade 3–4 neutropenia and febrile sequelae while maintaining a greater RDD following treatment. G-CSF prophylaxis is necessary for myelosuppressive chemotherapy patients, according to these data.

One of the most prevalent dose-limiting effects of cytotoxic chemotherapy in breast cancer is neutropenia. Severe neutropenia might delay treatment, reduce doses, hospitalize patients, and raise healthcare expenses, reducing efficacy. Its prolonged circulation half-life allows pegfilgrastim, a pegylated long-acting version of recombinant human G-CSF, to stimulate neutrophils and recover them with a single injection per treatment cycle. Previous research shows that pegfilgrastim effectively lowers chemotherapy-induced and febrile neutropenia in myelosuppressive chemotherapy patients (13).

Adequate chemotherapy dose intensity affects breast cancer treatment outcomes. Less than 85% of planned chemotherapeutic dose intensity leads to poorer clinical outcomes compared to full-dose therapy (12). Additional studies have further confirmed the association between reduced relative dose intensity and poorer survival outcomes in patients with breast cancer (14). In the present study, prophylactic pegfilgrastim allowed patients to maintain higher RD. Is during TC chemotherapy, suggesting that G-CSF prophylaxis may help preserve treatment efficacy by preventing chemotherapy interruptions.

Although pegfilgrastim effectively reduced neutropenia in our study, mild adverse effects such as bone pain, arthralgia, and myalgia were more frequently observed in patients receiving prophylactic pegfilgrastim. Common side effects of G-CSF therapy can be managed with symptomatic treatment (15).G-CSF therapy can cause large-vessel vasculitis and aortitis (16, 17). The study found no notable concerns with pegfilgrastim.

Previous studies have demonstrated that pegfilgrastim-supported chemotherapy may alter immune cell numbers. Researchers believe pegfilgrastim may help immune cells survive bone marrow-suppressing chemotherapy (18).

Preventing febrile neutropenia may simplify treatment, reduce healthcare costs, and reduce hematologic toxicity. Pegfilgrastim before chemotherapy reduces febrile neutropenia risk in cytotoxic chemotherapy patients (19). Preventing febrile neutropenia may reduce the need for broad-spectrum antibiotics.

Studies demonstrate that antibiotics during chemotherapy may affect gut flora, which may damage the immune system and treatment (20, 21). Preventive pegfilgrastim may reduce febrile neutropenia, antibiotic exposure, and gut flora imbalance. Recent advancements in immunotherapy and targeted therapies have enhanced the treatment landscape for triple-negative breast cancer (TNBC). The phase III KEYNOTE-522 trial demonstrated that the addition of pembrolizumab to neoadjuvant chemotherapy resulted in improved pathological complete response rates and event-free survival among early-stage TNBC patients (22). Furthermore, the KEYNOTE-355 and IMpassion130 trials indicated that immune checkpoint inhibitors, when combined with chemotherapy, yielded better outcomes for patients with metastatic TNBC (23, 24).

Patients with targeted medications have more therapeutic options. The OlympiA trial found that olaparib dramatically improved survival rates for germline BRCA-mutated breast cancer patients without invasive disease (25). Sacituzumab govitecan enhanced metastatic TNBC survival in the ASCENT trial (26) as well.

Despite these developments, cytotoxic chemotherapy is still the main TNBC treatment, especially before or after surgery. Clinical management involves administering chemotherapy effectively and minimizing side effects. Prophylactic pegfilgrastim and other supportive care help safely administer powerful chemotherapy.

Disease-free survival (DFS) rates were similar in both the PEG(+) and PEG(−) groups. The ability to determine long-term statistical results might be limited by the small sample size and the short follow-up period. To determine if using G-CSF before chemotherapy improves treatment results and extends life, more research is needed, including larger studies and longer follow-up periods.

This study has issues. The study's findings may be misleading because it only examined one institution. Survival outcomes may be tougher to detect due to the small sample size. Third, retrospective analysis may bias patient selection and negative reporting despite the widespread use of clinical data. Nevertheless, this trial furnishes essential clinical evidence that supports the use of pegfilgrastim prophylaxis in early-stage TNBC patients undergoing TC treatment.

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