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Research Article

Comparison of Pegfilgrastim with Filgrastim in Management of Chemotherapy Induced Neutropenia in Breast Cancer Patients

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Abstract
Background & Objective: *Granulocyte Colony Stimulating Factor (G-CSF) is a glycoprotein, helps in producing cells from bone marrow. Pharmaceutical analogs of naturally occurring G-CSF are used in chemotherapy induced neutropenia to prevent infections and sepsis. This study compares the efficacy and safety of single fixed dose of pegfilgrastim (pegylated form of filgratim) versus daily administration of filgrastim in breast cancer patients*
Patients and Method: *Patients (n=80) with confirmed diagnosis of breast cancer receiving chemotherapy regimen (cyclophosphamide+doxorubicin+paclitaxel) were randomised in 2 groups. One group received pegfilgrastim 6 mg subcutaneously & the other group received filgrastim 300 mcg consecutively for 3 days on day 2 of chemotherapy cycle.The primary end point was the occurrence of febrile neutropenia (neutrophil count <4000 and fever on same day or the day after).The secondary end points were duration of hospitalizations, intravenous (IV) antibiotics required for neutropenia, and episodes of anemia.*
Any adverse drug reaction (ADR) related to study drug were observed.
Results: *Forty patients were analysed in each group (176 cycles in group 1 & 197 cycles in group 2). Neutropenia developed in 5.6% & 11.6% (p<0.0423), mean duration of hospital stay were 3-4 days & 5-6 days, i.v antibiotic usage was4% & 7%. 25% of patients in group 1 and 29% in group 2 suffered from anemia and required blood transfusion respectively. Bone pain was the most common ADR found due to filgrastim.*
Conclusion: *Single dose of pegfilgrastim were significantly better than 3 doses of filgrastim for reducing Neutropenia rate in breast cancer patients receiving chemotherapy.*
Keywords: *G-CSF (Pegfilgrastim, filgrastim), Breast cancer, Neutropenia.*

Introduction

Chemotherapy targets rapidly proliferating cells and causes myelotoxicity as a frequent side effect.[i] Neutropenia is the major dose-limiting toxicity of many chemotherapy regimens, especially with the advent of the more efficacious chemotherapeutic regimens, e.g., taxane containing regimens for breast cancer.[ii,iii] Treatment induced neutropenia and its infectious complications can lead to persistent fever ('febrile neutropenia') requiring hospitalization, considerable cost escalations, reductions and or modification in chemotherapy

doses/ protocols (reduced relative dose intensity) and reduced survival rates over time.[iv,v] Risk of febrile neutropenia (FN) depends on the chemotherapy regimen and individual patient risk factors (e.g., age, type and stage of cancer, etc).[vi] The risk of infection increases with decreasing absolute neutrophil counts(ANC), i.e., in Grade 3 and grade 4 neutropenia (neutrophil count < 1000 µL and 500/µL respectively).[vii,viii] Such infections even when managed with only broad-spectrum antibiotics can lead up to 10% in-patient mortality[vii] Granulocyte colony stimulating factors (G-CSF) help increase absolute counts of functional and mature neutrophils in the circulation by reducing the transition time (proliferation, differentiation and activation from stem cell to mature neutrophil).[ix] Endogenous production of hematopoietic growth factors often fails to prevent chemotherapy induced myelosuppression necessitating supplementation with pharmaceutical analogues.[x] The most commonly used type of recombinant G-CSF is filgrastim.[7, xi]Over the time, credible clinical guidelines (ASCO, EORTC, NCCN) have defined increasingly liberal indications for administration of recombinant G-CSF for prophylaxis and management of febrile neutropenia[xii] mostly due to decreasing costs of these factors[xiii] and increasing evidence on their efficacy and economic advantages.[xiv] In India, prophylactic use of recombinant G-CSF has been a prevalent practice in patients on aggressive chemotherapy regimens for several reasons: lower standardized costs of G-CSF and hospitalization in comparison to that in developed countries, increasing costs of antibiotics and high risk of morbidity and mortality due to logistic and accessibility challenges.[xv] However, gaps in practices exist for administration of G-CSFs viz., non-compliance with the daily dosing requirement, optimum duration of therapy and need to initiate the therapy early (usually from the first cycle).[xvi]

Breast cancer is the most common cancer among women in India with an age adjusted incidence rate of 34.4 per 100,000 women (2012).[xvii] A large proportion of these women need chemotherapy due to delayed care seeking and inadequate treatment.[xviii,xix] Studies on use of G-CSF use in cancer survivors in India are scarce, even as it is widely perceived that G-CSF and broad-spectrum antibiotics are commonly used for prevention/ management of febrile neutropenia in cancer survivors (including those with breast cancer), mostly without following a fixed protocol.[xx] Availability of evidence is even more unlikely from the Empowered Action Group States, which show poor performance on health and human development indicators. We undertook this study to study the profile (demographic and clinical) of patients with breast cancer on chemotherapy receiving Filgrastim and Pegfilgrastim at an apex cancer institute for Eastern India situated in Cuttack, Odisha (one of the EAG states). Efficacy and safety profile were compared between pegfilgrastim & filgrastim on neutrophil counts in patients receiving simple (two-drug) and complex (more than two drug) chemotherapy regimens. We have also analysed the cost effectiveness of GCSF used in breast cancer patients.

Methods

Study Setting

This study was done at Acharya Harihar Regional Cancer Centre (AHRCC) Cuttack, Odisha by the Department of Pharmacology, Sriram Chandra Bhanja Medical College and Hospital, Cuttack, Odisha. AHRCC is one of the 27 RCCs of India. It is a 32 year old 281-bedded Odisha state-autonomous institution committed to the treatment, education, training and research related to cancer with advanced method and technologies. AHRCC contributes data to the Hospital Based Cancer Registry and Patterns of Care and Survival Studies in Cancer Cervix, Cancer Breast and Head & Neck Cancers (HBCR-POCSS) under the National Cancer Registry Programme. Several social and health security programs are run at AHRCC that makes it an affordable destination for cancer care seekers from Odisha and neighboring states. AHRCC is National

Accreditation Board for Testing and Calibration Laboratories (NABL) certified.

Study Population: The study population comprised of patients receiving chemotherapy for breast cancer in Odisha.

Study Duration: May 2016 to June 2017

Study Design: Prospective, Observational study

Methodology

With the permission from the Head, Department of Pharmacology and the respective Unit In-charge Faculty of wards at AHRCC, 'eligible' in-patient case sheets were analyzed and observed personally utilizing a prospective observational design under the clause of patient confidentiality and anonymity.

'Eligibility criteria' was defined as (i) female patient admitted to the in-patient female ward of AHRCC between 30th May 2016 - 30th June 2017 (both dates inclusive), (ii) a definitive diagnosis of 'breast cancer' (with or without FN), (iii) undergoing at least one cycle of chemotherapy, (iv) received G-CSF (Filgrastim or Pegfilgrastim) during the first injection of the index chemotherapy cycle and (v) provided verbal informed consent to participate in the study (for those who were currently admitted).

Exclusion criteria were- (i) Pregnant women (ii) stage 3 & 4 breast cancer patients (iii) patients who had undergone radiation therapy within 4 weeks of enrollment (iv) patients with secondary malignancy (v) bone marrow and stem cell transplantation.

The units primarily maintained three types of records: the in-patient case sheet that described the patient's clinical history, clinical and treatment course, the laboratory reports which helped in a serial enumeration of the performance of the patient's biochemical and hematological parameters and the discharge summary sheet which summarized the patient's diagnosis, key laboratory indices, management interventions and state of health at discharge. Consequently, records could be elicited from these patients till as early as March 2016 at AHRCC. Records of patients who have received at least one dose of G-CSF were taken into consideration; all cycles of chemotherapy were taken in to observation. Patients were observed personally during their stay in hospital and were divided into 2 groups for comparison purpose.

Patients receiving filgrastim injection PFS 300 mcg, a Recombinant Human Granulocyte Colony Stimulating factor (rHu G-CSF) administered subcutaneously up to maximum of three doses were in group II. Patients receiving pegfilgrastim (pegylated form of filgrastim) s.c. 6mg/0.6 ml single dose both 24 hours after of chemo regimen were in group I.

The routine investigations on all in-patient admissions at AHRCC usually included hemoglobin, total leukocyte count (TLC), differential leukocyte count (DLC), ANC, bacterial blood culture, and antimicrobial sensitivity of the isolate (if any). All routine investigations were done on day 1 of chemo cycle. Patients' body temperature (left axilla) was recorded daily besides vigilance for adverse events throughout the cycle. Blood samples for investigations were collected from the ante-cubital vein (preferably left arm). The investigations were conducted in the AHRCC laboratories. Rate of Neutropenia and other hematological ADRs were assessed as per Common Terminology Criteria for Adverse Events (CTCAEV 3.0) guidelines. Any ADR observed after administration of study drug was noted and causality assessment was done

Incidence of febrile neutropenia or Grade 4 neutropenia/ thrombocytopenia, anemia, use of intravenous antibiotics, duration of hospitalization, incidence of adverse events, and any requirement of blood transfusion were also recorded.

The study end points were as:

Primary End Point - The occurrence of Febrile Neutropenia (F.N) [A.N.C Count <1000 – 500/mm3<1.0 – 0.5 x 109 /L].

Secondary End Points- Duration of hospitalizations, intravenous (i.v) antibiotics required for neutropenia.

Episodes of anemia & thrombocytopenia and requirement of blood transfusion were also recorded. Any adverse drug reaction (ADR) related to study drug were also observed.

Information from the records was directly entered onto a Microsoft Excel 2010 spreadsheet. The spreadsheet was provided with automatic logic checks to prevent errors in data entry. Categorical variables were represented as frequency & proportion. Z score calculator was used for population proportion between 2 groups. Categorical values were expressed as frequency and proportion. Statistical significance was tested at $p<0.05$

The indicators on which the information was recorded included the name of the patient, age, weight, body surface area, registration number, regimen of chemotherapy, and number of injections of filgrastim received, any other intravenous drugs received , any blood transfusion received and the total number of cycles of chemotherapy received. The data was analyzed with Microsoft Excel 2010 and STATA v12.0. Numerical data was compared using Student's t-tests (paired).

Results

Demographic Profile

Present study was carried out on 80 breast cancer patients; with confirm diagnosis, in female ward of Acharya Harihar Regional Cancer Centre, Cuttack and HCG Panda Curie Cuttack, Odisha.

Analysis between GCSF analogues pegfilgrastim and filgrastim was done to compare the efficacy, safety and incremental cost effectiveness analysis of drugs. Forty patients were taken in each group.

The mean age was 46.9 years in group I (pegfilgrastim) and 45.7 years in group II (Filgrastim). The mean weight in group I was 58.1 ± 7.7 kgs and in group II was 56.3 ± 7.7 kgs.

53% of patients were <60kg in this study. Of the total 80 patients, 44% of patients have BSA (Body surface area) greater than 1.5 square meters while 39% of patients have greater than 1.5 square meters and 18% have 1.5 square meters.

The above mentioned details are presented in Table 3.1 and Figure 3.1 and 3.2.

Table Error! No text of specified style in document.**3.1:** Distribution w.r.t. Age Group

AGE -GROUP	GROUP I [PEG(n=40)]	Group II [FIL(n=40)]
25-35	9	8
36-45	11	15
46-55	12	11
56-75	8	7
MEAN	46.9	45.7

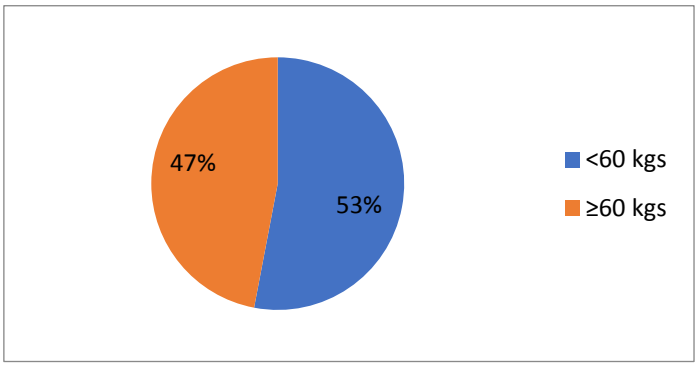

Figure Error! No text of specified style in document.**3.1:** Distribution w.r.t Weight

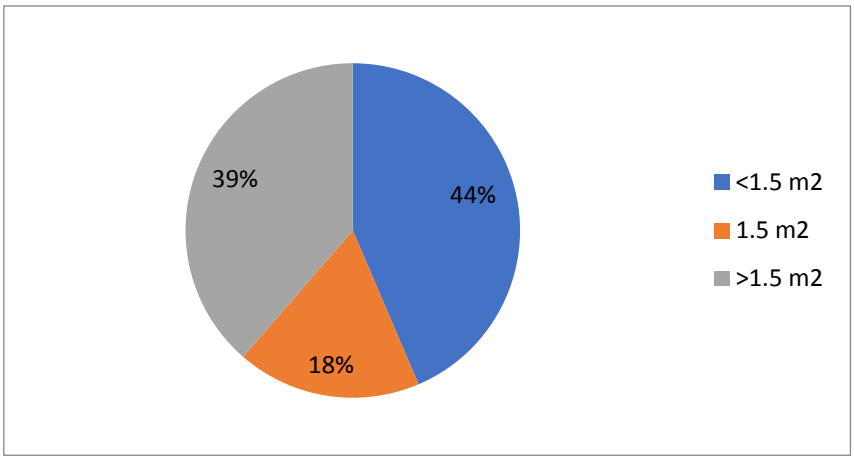

Figure Error! No text of specified style in document.**3.2:** Distribution w.r.t. Body Surface Area (BSA)

Clinical Profile

Of the total 80 patients, 42 patients (52.5%) have moderately differentiated cancer with score 7 according to Bloom Richardson Scoring system.

When the tumors were evaluated by immunohistochemistry (IHC) & by fluoroscent in situ hybridization (FISH) methods for receptor status, 33 patients (41%) were triple negative, i.e, ER-ve, PR-ve, HER2 neu –ve and 12 patients (15%) were triple positive, i.e, positive for all 3 receptors.

Her/neu status was positive in 11 patients (13.7%). Receptor status was unknown in 6 patients.

Clinical profile of the patients is given in Figure 3.3 and 3.4.

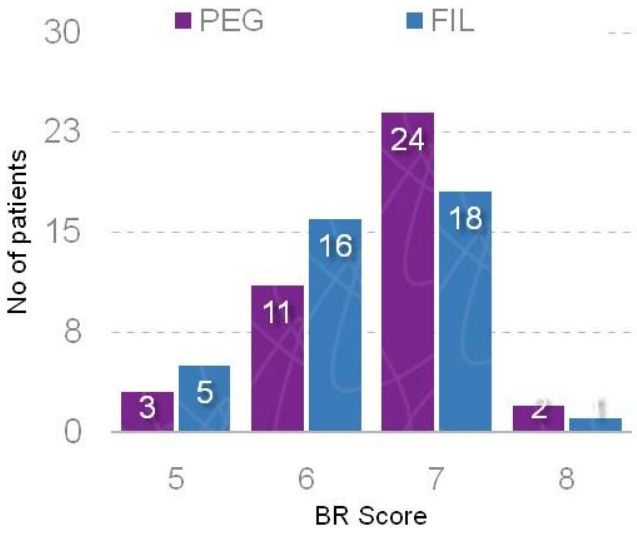

Figure Error! No text of specified style in document.**3.3:** Distribution w.r.t. Bloom Richardson Scoring System

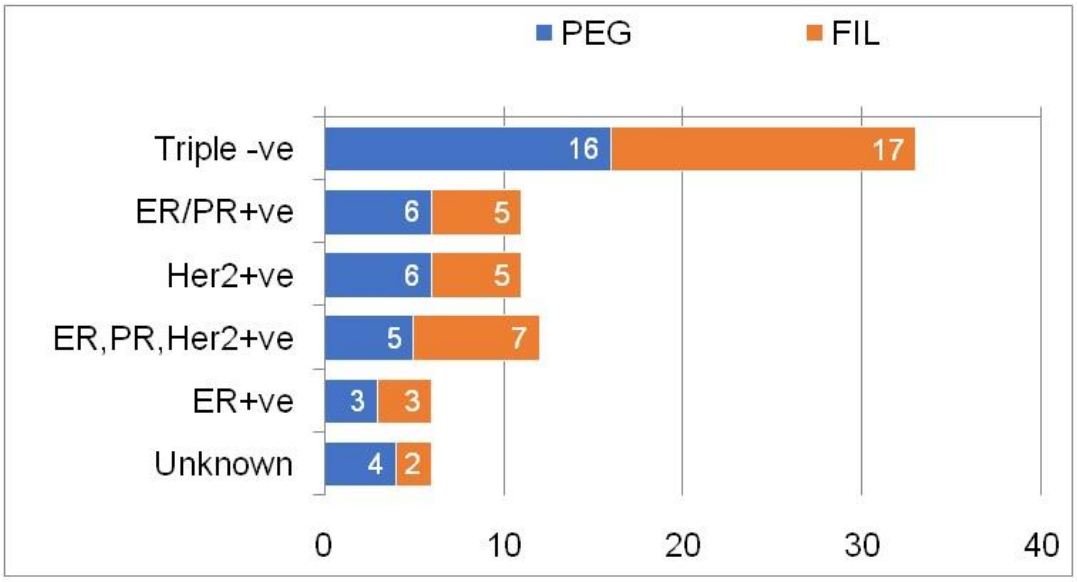

Figure Error! No text of specified style in document.**3.4:** Receptor Status of Patients

Treatment Profile

Most commonly used regimen in the patients were Cyclophosphamide+Doxorubicin followed by Paclitaxel followed by Transtuzumab (AC+T+Tt) in 20% patients. Second most common regimen used was TAC (Paclitaxel+Adiramycin+ Cyclophosphamide) in 18.7% patients.

All these details are represented in Figure 3.5.

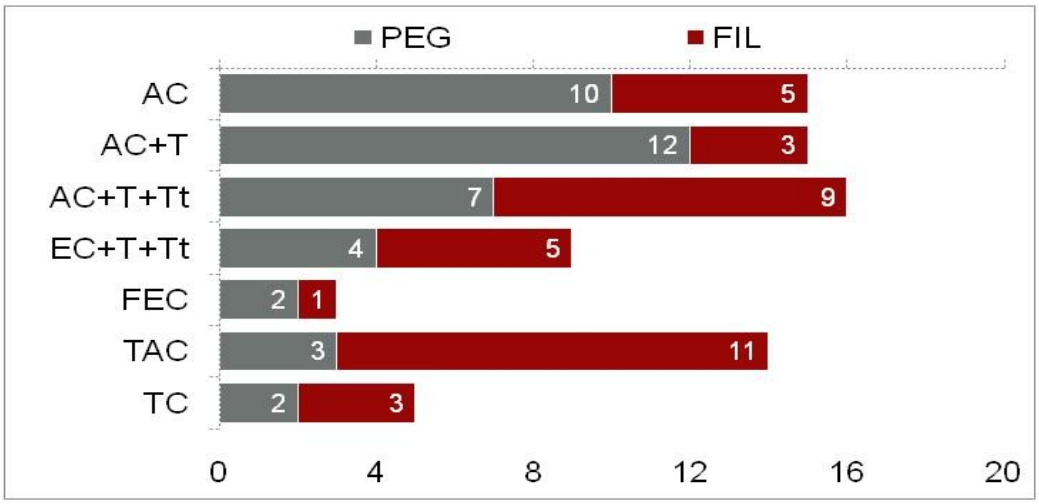

Figure Error! No text of specified style in document.**3.5:** Distribution Based on Treatment Regimen

Endpoint Analysis

Efficacy analysis was done in both the groups throughout each cycle of patients' chemotherapy which allowed for analysis of 176 cycles in group I (FIL) and 197 cycles in group II (PEG) patients. Each patient had undergone four (median value; mean: 3.7±1.7) cycles of chemotherapy. In group II each patient received about four (median value; mean: 4.2±2.7) courses of injection Filgrastim. In group I all patients received a single dose of pegfilgrastim.

Primary end point was episodes of febrile neutropenia among all cycles. Incidence of febrile neutropenia was 5.7% in pegfilgrastim group and 11.7 % in filgrastim group. Z score was used to calculate the significance between population

proportions among both groups. P value< 0.04 signifies that there were more incidences of febrile neutropenia in filgrastim group as compared to pegfilgrastim (Table 3.2).

Table Error! No text of specified style in document.**3.2:** Comparison of Incidence of Febrile Neutropenia

GROUP	CYCLES	Number of Episodes of F.N	Proportion (%)	P value	Z - Score
I. PEG	176	10	0.057 (5.7%)	p<0.04236	2.0348
II. FIL	197	23	0.117 (11.7%)		

Average duration of hospitalization was 3-4 days in group I (PEG) and 5-6 days in group II (FIL). Rate of i.v antibiotic administration were 4% in PEG group and 7.1% in FIL group (Table 3.3).

Table Error! No text of specified style in document.**3.3:** Comparison of Duration of Hospitalization and Intravenous Antibiotics Administration

GROUP	MEDIAN DURATION OF HOSPITALIZATION	% OF PATIENTS	RATE OF I.V. ANTIBIOTICS ADMINISTRATION
1. PEG	3 days	37%	4%
2. FIL	5 days	44%	7.1%

Mild anemia was present in 35 cycles of patients in group I & 39 cycles of patients in group II. Moderate anemia was present in 8 cycles in group I & in 15 cycles in group II. Severe anemia was present in 2 case in group I & in 5 cases in group II. Total blood transfusion requirement was 7 units in 7 cycles in group I and 33 units in 19 cycles in group II (Table 3.4).

Table Error! No text of specified style in document.**3.4:** Comparison of Anemia and Whole Blood Transfusion

GROUP	MILD	MODERATE	SEVERE	Total cases N(%)	B.T consumption no of cycles(units)
I**. PEG(176)**	35(20)	8(4.5)	2(1.1)	45(25.7)	7 (7 units)
II**. FIL(197)**	39(19.7)	15(7.6)	5(2.7)	59(29.9)	19 (33 units)

Safety Profile

The most common adverse drug reaction (ADR) was bone pains (32%) and least common ADR was drowsiness (5%). There were 2 & 4 reports of bone pain in group I & II respectively. In group I there was one report each of head reeling, drowsiness and anxiety. In group II there was 3 reports each of myalgia and anxiety and 2 cases each of backache and head reeling. Myalgia and head reeling had similar incidence of reporting (16%). 11% patients complained of back ache and drowsiness was reported in 5 % cases (Table 3.5).

Table Error! No text of specified style in document.**3.5:** Adverse Drug Reactions due to G-CSF Administration

ADRS	GROUP I	GROUP II	TOTAL (%)
BONE PAIN	2	4	32
BACKACHE	0	2	11
MYALGIA	0	3	16
HEAD REELING	1	2	16

DROWSINES	1	0	5
ANXIETY	1	3	21

Cost Effectiveness Analysis

Both PEG (pegfilgrastim) and FIL (filgrastim) group had 4 cycles of administration. PEG costs 5000 rupees per injection which was higher than per injection cost of FIL which is 1000 rupees, but cost of 3 injections of filgrastim / cycle was rounded to 3700 rupees. Expectedly cost per cycle is higher in PEG (5650 rupees) contrast to 3700 rupees in FIL.

To summarize the total cost of therapy is calculated to be 22600 rupees in PEG group and 14800 rupees in FIL group **(Table 3.6).**

Table Error! No text of specified style in document.**3.6:** Cost Comparison

GROUP	USAGE OF DRUG	COST / INJECTION	COST/ CYCLE	TOTAL COST
1. PEG	4 CYCLES	Rs 5000	Rs 5650	Rs 22600
2. FIL	4 CYCLES	Rs 1000	Rs 3700	Rs 14800

Incremental Cost Effective Ratio (ICER)

$$\textbf{ICER} = \frac{cost_A\ (\$) - cost_B\ (\$)}{effect_A\ (\%) - effect_B\ (\%)}$$

$$= \frac{22400 - 14800}{94.3 - 88} = 1300$$

Incremental Cost Effective Ratio (ICER)

$$ICER = \frac{cost_A\ (Rs) - cost_B\ (Rs)}{effect_A\ (\%) - effect_B\ (\%)}$$

[effectA - primary efficacy end point (F.N.) of pegfilgrastim in%
EffectB - primary efficacy end point (F.N.) of filgrastim in%]

ΔC = Cost difference between A & B

ΔE = Efficacy difference between A & B

ICER = 1300

$\Delta C = 1300 \Delta E$(F.N)

Although the cost of pegfilgrastim is higher, there is significant increase in effectiveness. The effectiveness is 1300 times as comparison in terms of cost

Discussion

Over the past few years the incidence of breast cancer is increasing & incidence of adverse drug reactions (ADRs) caused by these drugs are also increasing. Chemotherapy has proven to improve quality of life and prevent disease recurrence. Despite these therapeutic successes, many of the antineoplastic drugs possess narrow therapeutic index and a greater potential for causing adverse effects. In agreement to other studies, the highest incidence (39.1%) of ADRs was seen in patients undergoing treatment for breast carcinoma.[xiv,xxi] Studies carried out by Mallik *et al*. reported neutropenia as the most common ADR. Antimetabolites and alkylating agents were the most common drugs causing ADRs in Poddar *et al*. study[xxii]

The NCCN[xxiv] & ASCO[xxxi] guidelines for GCSF use have been revised to recommend routine growth factor administration with cycle 1 for chemotherapy regimens associated with a >20% risk of febrile neutropenia (F.N.), in patients who are at increased risk for serious toxicity, the risk of febrile neutropenia associated with regimen (NCCN guidelines)[xxiv]. With this background, efficacy and safety analysis between pegfilgrastim and filgrastim were done in 80 patients (40 patients in each group). The primary end point was incidence of febrile neutropenia and secondary end point was median duration of hospitalisation and i.v antibiotic administration in both groups. Severity of anaemia was also assessed in both groups.

According to literature F.N. is relatively common in breast cancer patients. Up to 23% of the breast

cancer patients experience at least 1 episode of F.N. during standard chemotherapy and this figure is increased upto 98% in patients exposed to high-dose chemotherapy regimens[xxv,xxvi]. The incidence of F.N. was 5.7 % in pegfilgrastim group in our study (Table 3.2) as compared to 14% in Homes et al study[xxvii], 13% in Green et al study[xxviii], 5% in G.von et al study[iii] and 1% in Vogel et al study[xxiv]. According to G.von Minck et al study[iii], the incidence of grade 3-4 neutropenia was 39% in pegfilgrastim group and 72% in filgrastim group.

Table Error! No text of specified style in document.**0.7:** Incidence of Febrile Neutropenia in Patients Receiving Pegfilgrastim with Chemotherapy for Breast Cancer

	Number of Patients	F.N INCIDENCE(%)
OUR STUDY	40	5.7
HOLMES et al	108	14
GREEN et al	77	13
VOGEL et al	463	1
G.VON et al	1303	39

In our study incidence of i.v antibiotic uses in both filgrastim & pegfilgrastim group were 7.1% & 4% respectively (Table 3.3). According to Green et al study[xxviii], i.v. antibiotic administration was 21% and 17% and hospitalization was 31% and 18% for the filgrastim and pegfilgrastim groups, respectively. In Vogel et al study, the IV anti-antibiotic use was lower in patients who received pegfilgrastim as compared with patients who initially received placebo (2% vs 10%) and the incidence of hospitalization was(1% vs 14%), respectively[xxix]

In this study mild anemia was observed in 20% pegfilgrastim and 19.7% filgrastim group respectively (Table 3.4) as compared to 3.3% in Lobil et al study[xxxiv]. Severe anemia was found in 1.1% pegfilgrastim and 2.7% filgrastim group respectively in this study (Table 3.4).

According to literature Holmes et al & Green et al, the use of pegfilgrastim from the first cycle significantly reduces the need for hospitalization and IV antibiotics, which parallels earlier reports of pegfilgrastim used to support more myelosuppressive chemotherapy[xxvii,xxviii]. The detected rate of febrile neutropenia observed in the initial placebo group is consistent with earlier reports of single-agent docetaxel without growth factor support[xxxii,xxxiii]

Chemotherapy regimens that are less myelosuppressive (i.e, rate of febrile neutropenia < 20%) are generally not administered with concomitant growth factor support. This practice is consistent with current guidelines from the American Society of Clinical Oncology (ASCO)[xxxi] that call for the use of a colony-stimulating factor in the first cycle of a cytotoxic chemotherapy regimen associated with a febrile neutropenia incidence of 40% or greater. However, Vogel et al study[xxix] shows that because the intensity of myelosuppression is reduced, as reflected in the incidence of 20%, febrile neutropenia can be markedly reduced by more than 94% with first-cycle use of pegfilgrastim.

The most frequent ADR related to GCSF was bone pain; 55% pegfilgrastim and 42% filgrastim in Green et al study[xxviii] as compared to 5% pegfilgrastim and 10% filgrastim in our study (Table 3.5). Bone pain occurred in 27% in the initial placebo group and 31% who received pegfilgrastim. In Papaldo et al study[xxx] the most frequently reported ADR were bone pain, which occurred in 46% patients.

The cost analysis was done taking into account the direct costs of GCSF and cost of its administration. Indirect, intangible cost and outpatient costs were not assessed. The direct costs were the total cost of injection of GCSF and cost of its administration. Cost of one injection of pegfilgrastim is more as compared to filgrastim, but filgrastim is given for subsequently minimum of 3 days which rounded to cost of Rs 3700 /- in one cycle. The difference between costs of drugs per cycle is not much as compared with efficacy.

The Incremental cost effective ratio (ICER) when calculated taking F.N. as efficacy end point, it was $\Delta C = 1300 \Delta E$(F.N) This value shows that although the cost of pegfilgrastim is higher, there is significant increase in effectiveness. The effectiveness is 1300 times as comparison in terms of cost

Limitation: Small sample size.

Conclusion

The incidence of febrile neutropenia is significantly less in pegfilgrastim group compared to the filgrastim group. Intravenous antibiotic administration and anemia were also less in pegfilgrastim group. On safety analysis, bone pains was found to be the most common ADR due to GCSF and was maximum in filgrastim group. On analysing cost, the ICER was 1300; indicating that effectiveness of pegfilgrastim was 1300 time more as compared to filgrastim in terms of cost.

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