Comparison of Short Acting versus Long Acting Filgrastim for Reduction of Chemotherapy Induced Febrile Neutropenia

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ABSTRACT

Introduction: Febrile neutropenia (FN) is the most frequent complications reported during cytotoxic chemotherapy treatment. Granulocyte colony stimulating factor (GCSF) is used to reduce neutropenia and related complications. This study compares short versus long acting filgrastim for reduction of chemotherapy induced FN.

Methods: Histologically confirmed solid cancer patients (n=112) receiving either high risk or intermediate risk chemotherapy regimens for FN were randomized into two groups. Group one received filgrastim 300 mcg subcutaneously for five days and group two received pegfilgrastim 6 mg subcutaneously single dose, starting after 24 hours after completion of chemotherapy during each chemotherapy cycle. The primary end point was the occurrence of FN. The secondary end points were number of hospital visits, duration of hospital stay and total direct costs of filgrastim and pegfilgrastim.

Results: Fifty six patients were analyzed in each group. The incidence of FN was significantly lower in pegfilgrastim group (42.90%) than filgrastim group (69.6%), p<0.004. The mean hospital visits were 1.84±1.93 in filgrastim group and 0.84±1.19 in pegfilgrastim group with 58.90% and 33.90% hospital admission respectively in both groups. The mean duration of stay was 4.14±3.69 days in filgrastim group and 2.36±3.35 days in pegfilgrastim group. The mean cost (Nepali rupees) of filgrastim and pegfilgrastim was 20162.50+6645.37 (US$168.17±55.42) and 32210.71±10429.43($268.67±86.99) respectively.

Conclusion: Single dose of pegfilgrastim was significantly better than multiple doses of filgrastim for reducing FN incidence in cancer patients receiving chemotherapy.

Keywords: Chemotherapy; Febrile neutropenia; Filgrastim; Pegfilgrastim.

INTRODUCTION

Chemotherapy induced neutropenia is a frequent complication of cytotoxic chemotherapy treatment. It increases the risk of infection and often lead to febrile neutropenia (FN).[1] Development of FN may compromise the treatment response with substantial economic burden.[2] Granulocyte colony-stimulating factor (GCSF) administration could prevent episodes of FN and its related complications.[3-5] Moreover, guidelines recommend that GCSF should be used where the risk of FN is considered.[6-8] Filgrastim and pegfilgrastim are GCSFs approved for the reduction of neutropenia-related outcomes.[9-11] Studies suggest that pegfilgrastim is more effective than filgrastim in reducing neutropenia-related outcomes.[12-15] In Nepal, there are no studies comparing the efficacy of GCSF's in FN occurrence and their related hospitalization outcomes along with their direct administration costs to the patients.

This study thus is aimed to compare short versus long acting filgrastim for reduction of chemotherapy induced febrile neutropenia and direct costs to cancer patients.

METHODS

A randomised comparative study was conducted at Bhaktapur Cancer Hospital and Bir Hospital in the department of oncology with the permission from Institutional Review Board, National Academy of Medical Sciences for 1 year period. The study population comprised of patients with histologically confirmed solid cancer, who were 18 years and above, receiving either high risk or intermediate risk chemotherapy regimen for FN[16] and those who were able to give written informed consent for participation.The Exclusion criteria were 1) Patients with neutropenia due to other causes (other than chemotherapy induced); 2) Patients with history of allergy to GCSF; and 3) Patient refusing to give consent. All the patients, fulfilling the eligibility criteria were enrolled in the study after written informed consent. Patient's clinical history, treatment course, the laboratory reports were recorded from the patient's case sheets either from out-patient department records or the discharge summary sheet. Standardized Performa were used to record the data in accordance with the protocol's instructions.

112 patient were enrolled in this study out of which 56 patient receiving short acting filgrastim and another 56 receiving pegfilgrastim were randomly selected in group one and group 2 respectively. Group 1 received short acting filgrastim and Group 2 received pegfilgrastim. Patients in filgrastim group had received a dose of 300 mcg/day, administered as a subcutaneous injection starting 24 hour after chemotherapy and continued daily for five days.[10] Patients in pegfilgrastim group had received a fixed dose of 6 mg as a single subcutaneous injection after 24 hour of chemotherapy of each cycle. FN was ascertained on a cycle-specific basis.

As per Infectious Disease Society Of America (IDSA) guideline, FN was defined as a single oral temperature measurement of >38.30C (101 0F) or a temperature of >38.00C (100.40F) sustained over a 1-h period with an Absolute Neutrophil Count (ANC) of <500 cells/mm3 or an ANC that is expected to decrease to <500 cells/mm3 during the next 48 hours.[17]

Patients receiving chemotherapy regimen with high risk for FN (>20%) had received primary prophylaxis with GCSF regardless of the risk factors. For patients receiving chemotherapy regimen with intermediate risk for FN (10-20%) had received prophylaxis with GCSF if > 1 patient specific risk factors are present. High risk regimen, Network guideline for neutropenia.[16] Follow up evaluation was done on day seven following chemotherapy of each treatment cycle or on as required basis throughout the chemotherapy cycle. ANC count was noted during each follow up and prior to chemotherapy cycle. Patients themselves recorded their body temperature daily, and were monitored for adverse events throughout the study. Formal risk classification was performed using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system.[7] High-risk patients (MASCC score <21) was admitted to the hospital and Low-risk patients (MASCC score >21) were candidates for oral and/or outpatient therapy. Patient were managed according to the IDSA guidelines for FN.[17] The direct total cost of GCSF of each group for each cycle was noted and summed up at end of treatment cycle. The data were entered using Statistical Package for the Social Sciences (SPSS) software version 20.0. Statistical analysis was done using SPSS software after entering the data on a master chart. Data were analyzed using descriptive statistical methods. Association between febrile neutropenia and selected variable were assessed using chi-square test and differences in score of filgrastim and pegfilgrastim had been analyzed based on selected variables using independent t-test at 95% confidence level.

RESULTS

Fifty six (56) patients were taken in each group. The mean age was 52.59+13.65 years in group 1 and 51.04±14.77 years in group 2. The total mean age was 51.81±14.18 years with age range from 18-77 years. In group 1, 73.20% were female whereas 75.00% were female in group 2. In this study, breast cancer had the highest number of cases. (Table 1)

Table 1: Demographic and clinical profile

Demographic and clinical variable	Filgrastim (group 1) n=56(%)	Pegfilgrastim (group 2) n=56(%)	Total
Age (mean years ±SD) (range)	52.59+13.65 (18-75)	51.04+14.77 (24-77)	51.81+14.18 (18-77)
Sex			
Male	15 (26.80%)	14 (25.00%)	29 (25.89%)
Female	41 (73.20%)	42 (75.00%)	83 (74.11%)
Cancer type			
Breast	10 (17.85%)	29 (51.78%)	39 (34.82%)
Gastrointestinal (GI)	21 (37.50%)	7 (12.50%)	28 (25.00%)
Genitourinary	2 (3.57%)	3 (5.35%)	5 (4.46%)
Gynaecological	10 (17.85%)	5(8.92%)	15 (26.78%)
Others	13 (23.21%)	12 (21.42%)	25 (22.32%)

Most commonly used regimen in the patients was Docetaxel+Adriamycin+Cyclophosphamide (TAC) in 24.10% patients. Second most common regimen used Gemcitabine + Carboplatin in 12.50% followed by Paclitaxel + Carboplatin in 11.60% and Adriamycin+Cyclophosphamide, Paclitaxel (ACT) in 9.80% patients.(Figure 1)

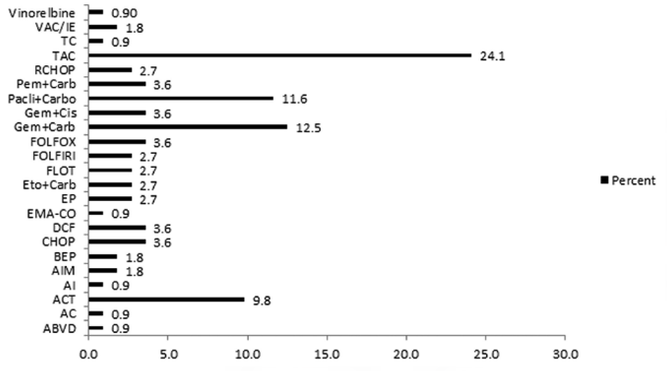

Figure 1: Types of chemotherapy and percentage

Efficacy analysis was done in both the groups throughout each cycle of patient's chemotherapy course, which allowed for analysis of 317 cycles in group 1 and 310 cycles in group 2 patients. Each patient had undergone 5.60 ± 2.12 cycles of chemotherapy on an average. In group 1 each patient received 3.23+2.56 courses of injection filgrastim. In group 2 all patients received a single dose of pegfilgrastim. Primary end point was episodes of FN among all cycles. Incidence of FN was 69.60% in group 1 with mean FN episode of 3.21+2.82.

Table 2: Endpoint analysis on both group

Endpoint	Filgrastim (Group 1) n=56 (%)	Pegfilgrastim (Group 2) n=56 (%)	p value
Febrile neutropenia (FN)	39 (69.60)	24 (42.90)	0.004*
FN episode (mean ± SD)	3.21 ± 2.82	1.43 ± 2.02	<0.001†
Admission	33 (58.90)	19 (33.90)	0.008*
Duration of stay (mean days ± SD)	4.14 ± 3.69	2.36 ± 3.35	0.009†
Number of visits (mean ± SD)	1.84 ± 1.93	0.84 ± 1.19	<0.001†
Total cost NPR(mean ± SD)	20162.50 ± 6645.37	32210.71 ± 10429.43	<0.001†

In group 2, FN incidence was 42.90% with mean FN episodes of 1.43±2.02. p value < 0.05 signifies that there were more incidences of FN in group 1 as compared to group 2. (Table 2)

The mean hospital visits were 1.84±1.93 in group 1 and 0.84+1.19 in group 2 with 58.90% and 33.90 % hospital admissions respectively in each group. The mean duration of stay was 4.14±3.69 days in group 1 and 2.36±3.35 days in group 2. The average cost of filgrastim was Nepali Rupees (Nrs.) 20162.50+6645.37 (US$168.17±55.42) and 32210.7 14±10429.43(US$268.67±86.99) for pegfilgrastim.

DISCUSSION

In this study, 112 patients were randomized to receive chemotherapy regimen with moderate to high risk of FN. The total mean age of the patient was 51.81 ± 14.18 years with range of 18-77 years and majorities (74.11%) were female. Among the cancer types, breast cancer had the highest incidence 34.82%, which was consistent with the population based cancer registry study (2018) in which the commonest site of cancer in females was breast (22.90%) in Kathmandu Valley.[18] In our study TAC regimen (Docetaxel, Adriamycin and Cyclophosphamide) was the most frequently used chemotherapy regimen (24.10%) followed by gemcitabine based regimen (16%) and dose dense AC (doxorubicin and cyclophosphamide) followed by T (paclitaxel) (9.80%).

In our study, incidence of FN in filgrastim group was 69.60% and in pegfilgrastim group was 42.90%. In a meta-analysis by Rastogi et al.[19] ,the incidence of FN in patients receiving filgrastim as primary prophylaxis ranged from 1% to 38%. Similarly, in prior studies by Holmes et.al.[20] and Green et.al.[21], the incidence of overall FN in filgrastim group was 18% and 20% and in pegfilgrastim group was 9% and 13% respectively. As compared to these studies our study had higher FN incidences in both the groups. The higher incidence of FN in our study might be because of included sample in which most of the patients were above 50 years, female, with breast and GI cancer and receiving highly myelosuppressive chemotherapy regimen. These risk factors correlated with the increase risk of developing FN as shown in a systematic review of literatures by Lyman et al.[22]

Although our study demonstrated higher incidence of FN in both the groups, the significant association of lower incidence of FN in pegfilgrastim as compared with filgrastim (p=0.004) was consistent with prior systematic review and meta-analysis by Cooper et.al.[23] and Kuderer et.al.[24] suggesting that primary prophylaxis with pegfilgrastim is more efficacious than filgrastim in reducing FN and its episodes. The decrease incidence of FN in pegfilgrastim group might be due to its longer half-life and presumed constant stimulation of neutrophils and neutrophil precursors in bone marrow and blood.

A study by Weycker et.al.[25] which concluded that FN remains a common complication among patients receiving myelosuppressive chemotherapy and results in extended hospitalization. In our study we found that the number of hospital visits (1.84±1.93 vs 0.84+1.19; p<0.001), hospital admission (33% vs 19%; p=0.008) and length of hospital stay (4.14±3.69 vs 2.36+3.35; p=0.009) was significantly higher in filgrastim group than pegfilgrastim group. These were consistent with the existing studies by Holmes et al.[22] and Green et al.[23] that the use of pegfilgrastim from the first cycle significantly reduced the need for hospitalization, number of visits and length of stay. These findings suggest that the primary prophylaxis with pegfilgrastim is more efficient for hospitalization related outcomes in prevention of neutropenia and its related complications. This could indirectly be beneficial to the patients in terms of hospital related morbidities and financial distress.

In this study, we found that total direct cost of pegfilgrastim was higher than filgrastim (NRs.32210.71±10429.43 vs NRs. 20162.50±6645.37; p<0.001) during total duration of treatment. This finding was consistent with the study by Rout et al.[26] in which the author found that costs per dose of pegfilgrastim was higher than multiple doses filgrastim per cycle of chemotherapy regimen. Although in our study the cost for pegfilgrastim was significantly higher than the filgrastim group, the indirect, intangible cost and outpatient costs were not assessed. These factors could have added more costs in filgrastim group as there were significantly more number of hospital visits, admission and more duration of admission in filgrastim group. Hence, considering these indirect costs to the patients', the use of pegfilgrastim could be more cost effective than filgrastim as shown by various previous studies.[26-29]

CONCLUSION

Febrile neutropenia is a common complication in cancer patients receiving myelosuppressive chemotherapy and typically results in extended hospitalization. Single dose of pegfilgrastim is better than multiple doses of filgrastim in reducing FN incidence which minimizes hospital stay, visits and frequency of admission in cancer patients receiving chemotherapy. Taken together, the adequate evaluation of patients and the use of prophylactic GCSF's become relevant for optimizing clinical outcomes and reducing hospitalization related morbidities in the management of FN. filgrastim group, the indirect, intangible cost and outpatient costs were not assessed. These factors could have added more costs in filgrastim group as there were significantly more number of hospital visits, admission and more duration of admission in filgrastim group. Hence, considering these indirect costs to the patients', the use of pegfilgrastim could be more cost effective than filgrastim as shown by various previous studies.

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