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Incidence and Risk Factors for Breakthrough Febrile Neutropenia in Cancer Patients Receiving Chemotherapy and Prophylactic Pegfilgrastim

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Abstract: ***Background: Hematopoietic growth factors (HGFs) reduces the risk of febrile neutropenia (FN) by about 50% in cancer patients receiving chemotherapy. However, breakthrough febrile neutropenia (BTFN) is still a potentially serious complication despite the use of HGFs. Objectives: We aim to investigate the frequency of BTFN and its risk factors in Middle Eastern cancer patients receiving prophylactic pegfilgrastim after cytotoxic chemotherapy. Materials and Methods: All consecutive patients with solid tumors who received pegfilgrastim either in primary or secondary prophylaxis settings from Jan 2009-Dec 2010 were retrospectively identified.Medical record (electronic and paper based) were reviewed. Incidence of BTFN was calculated as (number of episodes of BTFN/total number of injections of pegfilgrastim x 100). Following variables were analyzed using chi-square test for their association with the development of BTFN: age, sex, comorbidities, stage of disease, curative vs. palliative treatment, and serum albumin. Results: One hundred and eighty three patients were identified. Forty patients (21.9%) developed one or more episode of BTFN. Total number of administered pegfilgrastim injections was 581. Forty nine episodes of BTFN occurred resulting in an incidence of 8.4%. None of the above analyzed variables were found to be a significant risk factor for the development of BTFN. However, low serum albumin level showed a trend towards significance (p=.06). Conclusion: Incidence of BTFN after the use of pegfilgrastim in this patient population was found to be 8.4%. The possibility of association with low serum albumin warrants further investigation.***

Keywords: breakthrough febrile neutropenia, chemotherapy, pegfilgrastim

1. Background

Febrile neutropenia (FN) after the use of myelosuppressive chemotherapy is one of the common complications of cancer treatment (1, 2).Granulocyte colony- stimulating factor (G-CSF) has been proven to be an effective prophylaxis against FN. Pegfilgrastim, a long acting granulocyte colony-stimulating factor predominantly eliminated through neutrophil-mediated clearance is increasingly used prophylactically due to its effectiveness and convenience (3, 4, 5). Breakthrough febrile neutropenia (BTFN) is defined as the occurrence of FNdespite theuse of G-CSF prophylaxis (6).The reported incidence of BTFN in Western and Far - East Asian population is 4-17 % (5, 6). Only few studies have explored the risk factors predisposing to BTFN (7, 8). To our knowledge, incidence of BTFN in Middle Eastern patient population has not been studied. Therefore this study was conducted to determine the incidence of BTFN and identify possible clinical and laboratory risk factors.

2. Methods

Pharmacy prescription database was retrospectively searched to identify all consecutive adult cancer patients undergoing chemotherapy treatment between Jan 2009-Dec 2010. Patients who received at least one dose of pegfilgrastim either in primary or secondary prophylaxis settings were selected and are the subject of this study. Paper and electronic medical records of these patients were reviewed. Patients and tumor characteristics, details of chemotherapy, pegfilgrastim use, laboratory data and episode of FN were extracted.

Pegfilgrastim was given as single 6-mg subcutaneous injection, 24-48 hours after the use of myelosuppressive chemotherapy.The definition of neutropenia varies from institution to institution, but for our study BTFN was defined as an ANC $<1 \times 10^9$/l with a coincidental oral temperature ≥38 °C ,(100.4°F) despite the administration of pegfilgrastim prophylaxis. Incidence of BTFN was calculated as (number of episodes of BTFN/total number of injections of pegfilgrastim x 100).

Potential risk factors including age, gender, comorbidities, chemotherapy regimen, serum albumin, disease stage and intent of treatment (curative vs. palliative), were analyzed using chi-square test.Patients with leukemias and those undergoing stem cell transplant were excluded. Institutional Ethics committee approval was obtained for this study.

3. Results

One hundred and eighty three patients received at least one dose of pegfilgrastim during the study period. One hundred and twenty patients (65.5%) were female. Median age was 45 (14-85) years. Patients had the following diagnoses: breast cancer 60 (32.78%), lymphomas 60 (32.78%) and

other miscellaneous solid tumors 63 (34.43%).Patient characteristics are summarized in Table 1.

In total, patients received 581 injections of pegfilgrastim. Mean number of injections per patient was 3 (range 1-11). Forty out of 183 patients (21.9%) developed one or more episode of BTFN. Forty nine episodes of BTFN occurred resulting in an incidence of 8.4% (49x100 /581 = 8.4%).Age, gender, presence of comorbidities, chemotherapy regimen, stage of cancer, curative vs. palliative intent of treatment were not identified as significant risk factorsfor BTFN. Low serum albumin was associated with a trend for the development of BTFN (Odds Ratio: 2.36, P=0.06) (Table 2).

Table 1: Patients Characteristics

Characteristic	*N (%)*
Age ≥ 60	35 (19.13)
Sex Male	63 (34.42)
Tumor site Breast cancer	60 (32.78)
Lymphoma	60 (32.78)
Miscellaneous	63 (34.43)
Disease stage Advanced stage	132 (72.13)
Early stage	51 (27.9)
Intent of treatment Curative	127 (69.39)
Palliative	56 (30.6)
Comorbidities Present	48 (26.23)
Serum albumin Normal (≥38 g/L)	153 (83.61)
Low	24 (13.11)
Chemotherapy regimen Single agent	21 (11.47)
Combination	154 (84.15)
Palliative	31 (16.1)

Table 2: Risk factors contributing to BTFN

Factors	*BTFN Number (%)*	*Odds Ratio*	*P Value*
Age ≥60	9 (25.7)	1.31	0.539
<60	31 (20.9)		
Gender Male	14 (22.2)	1.03	0.931
Female	26 (21.7)		
Comorbidities Present	14 (29.2)	1.73	0.154
Absent	26 (19.3)		
Chemotherapy regimen	7 (33.3)		
Single agent	33 (21.4)	1.83	0.223
Combination			
Serum Albumin Low	9 (37.5)	2.36	0.06
Normal	31 (20.3)		
Stage of Cancer Early	10 (19.6)	0.83	0.690
Advanced	13 (22.7)		
Intent of Treatment Curative	9 (24.4)	1.67	0.208

4. Discussion

FN is a serious complication of myelosuppressive chemotherapy. Development of FN can lead to serious morbidity, chemotherapy dose reduction, treatment delays, decreased quality of life, hospitalization and use of financial resources (9, 10). Therefore, strategies for minimizing complications of neutropenia are needed. By stimulating neutrophil proliferation and differentiation, G-CSF including pegfilgrastim was shown to be effective prophylaxis against FN (11, 12). The American Society of Clinical Oncology (ASCO) guidelines justify the use of G-CSFwhen therisk of FN is ≥20%. They also recommend primary prophylaxisfor the prevention of FN in patients who are at high risk based on age, medical history and disease characteristics. (13).

FN after the administration of G-CSF is recognized in routine clinical practice, well documented in the literature and is labelled as BTFN (5, 6).To our knowledge this is the first published study that evaluated the incidence of BTFN in Middle Eastern patients. It will be unlikely that there will be any significant difference in efficacy and metabolism of pegfilgrastim in our patientscompared with other Asian and non-Asianpopulation.

Our data shows that BTFN incidenceis8.4% which is quite similar to what has been reported in western patient population. Morrison VA et al reported BTFN in 6.5% of patients who received filgrastim vs. 4.6% in those who received pegfilgrastim among patients treated with a heterogeneous group of chemotherapy regimens in community oncology practice in USA (14). A systematic review published recently by Fernandes R et al have reported median BTFN rate of 6.6% in patients receiving Docetaxel –cytoxan chemotherapy for breast cancer (15).

We were unable to identify patients' groups who are at higher risk of developing BTFN. Slightly over one fourth of patients (26%) had at least one comorbidity. Patients with comorbidities had slightly higher incidence of BTFN (29.2 % vs. 19.3%) but it was statistically not significant (95% CI 0.811-3.674, p= 0.112). Nevertheless, there was a noticeable trend in those with low serum albumin (Odds Ratio: 2.36, P=0.06). Lack of statistical statistically significant could be due to low number of patients in our study. Low serum albumin indicates low nutritional status and poor general health of patient and perhaps increased risk of infections. Morrison VA et al has also reported a low baseline serum albumin that was the only patient characteristic significantly associated with the incidence of FN (p=0.011) (14)OR 1.83, 95% CI 1.16-2.90

Several limitations can be considered when interpretatingthe results of our study. (1) It is possible that weunderestimated the incidence of BTFN as some patients may have presented to other hospitals with FN. (2) Information about prophylactic oral antibiotics were not collected. (3) Retrospective nature of the studyand a relatively small sample size. Our study also did not explore episodes of neutropenia without fever, as this can also delay the

treatment and can have negative impact on cancer management.

5. Conclusion

Our data indicates that there is still a considerable risk of developing FN after the use of pegfilgrastim particularly in patients with low serum albumin. Medical community and patients have to be aware of this risk. Further larger studies are needed to establish risk factors of BTFN, as close surveillance of these patients may improve clinical outcomes.

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