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Prophylactic Use of Granulocyte Colony Stimulating Factor (G-CSF) in Febrile Neutropenia- A Single Institutional Study.

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Abstract

Background: Breast cancer is the most common cancer among women in India and most of the patients need chemotherapy (CT) as a part of multimodal management. CT induced febrile Neutropenia (FN) causes unnecessary treatment interruptions which may have negative impact on disease outcome, besides unwanted hospitalization, treatment costs and high mortality rates.

Methodology: Sixty-six female breast cancer patients with early and locally advanced disease were started on various chemotherapeutic (CT)regimens after excluding 11 patients .The various regimens used were having risk of FN hence, were started on prophylactic granulocyte colony stimulating factors (G-CSF) (Filgrastim) 5 microgram/ KgBW subcutaneously (SC) after 24hours of completion of CT consecutively for five days. The main purpose of the study was to prevent neutropenia (febrile or afebrile) and its associated morbidity. Also the intention of the study was to complete CT on scheduled time, without unnecessary treatment delays and dose reductions which could have strong impact on disease outcome, patient's survival, costs and hospitalizations as well as mortality associated with it.

Results: The mean age of the patients was 48.77± 9.69 years. Four of 27 (14.81%) patients on TAC protocol developed FN out of which three had grade 3, and only one had grade 4 FN and required hospitalization. Three of 39 (7.69%) patients on other CT protocols, developed FN and was of grade 3, making a total of seven (10.6%) out of 66 patients.

Conclusion: This study concluded that although 10.6% patients showed FN despite of G-CSF prophylaxis, the grade of FN was less severe (grade 3) in majority of patients and were managed and recovered well from the neutropenia on outpatient basis. Hence, we recommend the prophylactic use of G-CSF as it decreases the incidence and severity of life threatening neutropenia.

Keywords: febrile neutropenia, myelosuppression, breast cancer, chemotherapy, granulocyte colony stimulating factor.

Introduction

Breast cancer is the second most common cancer among women in India and accounts for 7% of global burden of breast cancer and one-

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fifth of all cancers among women in India[1].Breast cancer is emerging as a major concern in female populations of the Kashmir valley with its incidence showing an increasing trend[2].Most of the patients are diagnosed in the stages where multimodality intervention is needed including CT, and the CT being not without any side effects, the dreaded of which is FN, which is not only a major risk factor for morbidity and mortality in patients with cancer but its occurrence, can also lead to a decision to reduce the CT dose as well as delay subsequent treatment cycles. Such treatment modifications are a concern when CT is given with curative intent and hence the importance of FN prevention [3, 4, 5, 6], besides leading to increased hospitalizations and intravenous (IV) antibiotic use [7].

The risk of developing FN depends on the degree and duration of CT-induced neutropenia and on several patient factors, including age, comorbidity and serum albumin levels [5].
FN can be prevented through the prophylactic use of hematopoietic cell growth factors (e.g., granulocyte colony-stimulating factors, G-CSF) – a strategy supported by current guidelines for patients deemed to be at high risk of FN (The indications for prophylactic administration of G-CSF are based on various risk factors, including the degree of myelosuppression associated with the CT regimen, and specific patient characteristics [3, 6].

FN, generally defined as fever (single oral temperature ≥38.3°C or ≥38.0°C for >1 h) with grade 3/4 neutropenia (absolute neutrophil count [ANC] <1.0 or <0.5×109/l), is associated with substantial morbidity, escalation of costs and mortality risk [6].

Most of the recently European Organization for Research and Treatment of Cancer (EORTC)-reviewed evidence indicates that primary and secondary G-CSF prophylaxis enabled the maintenance of CT dose and dose intensity [7].
Prophylaxis with recombinant G-CSF reduces the severity and duration of CT-induced neutropenia and the consequent risk of FN and is playing an increasingly broad role in supporting the delivery of myelosuppressive CT [6].

Materials and Methods

This prospective study was conducted in the department of radiation oncology for a period of 18 months from 2012 to 2013 and included total of 77 female Breast cancer patients and eleven patients were excluded from the study (four refused to consent, six did not afford the G-CSF prophylaxis and one was having cardiac comorbidity with ejection fraction of <50).Only 66 female breast cancer patients with early (T2N1) and locally advanced disease (T2/T3N2/N3)who were given various CTR (TAC: docetaxel75mg/m^2 IV day 1+Adriamycin 50 mg/m^2 IV day 1+cyclophosphamide 500 mg/m^2 IV day 1 repeated every 21 days for a total of 6 cycles; FEC: 5-Fluorouracil (5-FU) 500mg/m^2+epirubicin 500mg/m^2 +cyclophosphamide 500mg/m^2 IV repeated every 21 days; AC+T: Adriamycin 60mg/m^2 IV day 1+cyclophosphamide 600mg/m^2 IV day 1 repeated every 21 days for 4 cycles followed by Docetaxel 100 mg/m^2 IV on day 1 cycle repeated every 21 days for 4 cycles; CMF: Cyclophosphamide 600 mg/m^2IV day1 +Methotrexate 40 mg/m^2 IV day 1 and 8+5-fluorouracil 600mg/m^2 IV days 1 and 8 cycled every 28 days for 6 cycles) having risk of getting FN.

The patients included in the study were either a),CT naïve and were started on different CT regimens having a risk of FN>20% or those having risk of FN <20% but, were associated with other coexisting conditions, like poor performance score, old age (age >60 years),or had previous history of hospitalization for some other cause and had received G-CSF as primary prophylaxis or .b), those patients who developed episode of FN after exposure to first or second cycle of CT despite the CT regimen having a risk of FN of <20%,), G-CSF as secondary prophylaxis.

Table 1: Age characteristics, Stage of disease, severity of Febrile Neutropenia, length of hospital stays.

		Total Number, n/N (%)	Developed FN, n/N (%)
Age group in years	21-30	3/66 (4.54)	0
	31-40	9/66 (13.63)	1/66(1.51)
	41-50	20/66 (30.30)	2/66(3.03)
	51-60	29/66 (43.93)	4/66(6.06)
	≥61	5/66 (7.57)	0
Total Number, N		66	7/66(10.60)
Minimum Age in Years		21	
Maximum Age in Years		66	
Age in Years (Mean ± SD)		48.77± 9.69	
Stage II		39/66 (59.09)	
Stage III		27/66 (40.90)	
Developed Febrile Neutropenia		7/66 (10.60%)	
Severity of FN	Grade 3	6/66(9.09)	
	Grade 4	1/66 (1.51)	
Duration of hospital stay (in days)		6	

N = Total number of patients; n = number of patients; %= percentage; FN = febrile neutropenia; SD= standard deviation

The main purpose of the study was to prevent neutropenia (febrile or afebrile)in patients treated with curative intent to maintain the patients on various CT regimen protocols on scheduled time without unnecessary treatment interruptions and dose reductions which would have strong impact on treatment outcome, besides reduces the mortality/morbidity and unwanted hospitalization and costs associated with its management.

The data collected was analyzed and descriptive statistics involved mean and standard deviation for continuous variables and percentages for categorical variables.

Results

The mean age of the patients was 48.77± 9.69 years with age ranging from 21-66 years. About age distribution, four patients in 6th decade (51-60 years) and two patients in 5th decade (41-50 years) and one patient in fourth decade (31-40 years) developed FN. [Table 1] Patients had stage II (n=39/66) disease followed by stage III (n=27/66) [Table 1 and Table 2].

A total of seven patients developed febrile neutropenia (with or without fever), despite on G-CSF prophylaxis. Severity of FN was grade 3 in six patients and grade 4 in one patient with duration of hospital stay of six days in grade 4 Neutropenia [Table 1].

The stage-based analysis revealed that none developed FN in stage IIA, three patients in stage IIB, two patients in stage IIIA and one each in IIIB/IIIC developed FN respectively [Table 2].

Table 2: Stage of Disease at Presentation.

		Total	No FN, n/N (%)	Developed FN, n/N (%)
Stage of Disease at Presentation	Stage IIA	16	16/66 (24.24)	0
	Stage IIB	23	20/66 (30.30)	3/66 (4.54)
	Stage IIIA	11	9/66 (13.63)	2/66 (3.03)
	Stage IIIB	10	9/66 (13.63)	1/66 (1.51)
	Stage IIIC	6	5/66 (7.57)	1/66 (1.51)
Total		66	59/66 (89.39)	7/66 (10.60)

N = Total number of patients; n = number of patients; %= percentage, FN =febrile neutropenia

Table 3: Predisposing Factors for Febrile Neutropenia

Predisposing Factors for FN	Total	No FN, n/N (%)	Developed FN, n/N (%)
None	39	33/66 (50)	6/66 (9.09)
Poor Performance Score (PPS) of 2	14	14/66 (21.21)	0
Previous Episode of Febrile Neutropenia (PEFN)	5	4/66 (6.06)	1/66 (1.51)
Age 60 years or above	6	6/66 (9.09)	0
Hospitalization	2	2/66 (3.03)	0
Total	66	59/66 (89.39)	7/66 (10.60)

N = Total number of patients; n = number of patients; %= percentage, FN = febrile neutropenia

Regarding predisposing factors for FN only one patient was having predisposing factor for FN, developed FN, the rest of six patients who developed FN had none of the predisposing factors [Table 3].

Regarding the ECOG performance status, none of the patients with zero and two (total of nine with PS zero and 16 with PS of two) developed FN, and seven patients out of 41 with performance status of one developed FN [Table 4].

Regarding the risk of FN, three patients with risk of FN< 20% developed the FN and four patients with risk of FN≥20% developed FN [Table 5].

Twenty seven patients were on TAC protocol, out of which four (6.06%) patients developed FN and the severity of FN was grade 3 in three and grade 4 in one[Table 6]. Among 39 patients who were on other CT protocols, having the risk of developing FN<20%, but were associated with other predisposing conditions, three(4.54%) patients developed FN and all had grade 3 FN [Table 1 & 6].The only patient with grade 4 FN needed hospitalization and the duration of hospital stay was less than a week [Table 1].

Discussion

Neutropenia is a major dose-limiting toxicity of myelosuppressive CT that predisposes patients to serious infections. FN, generally defined as a fever (single oral temperature ≥38.3°C or ≥38.0°C for >1 h) with grade 3/4 neutropenia (absolute neutrophil count [ANC] <1.0 or <0.5×109/l), is associated with substantial morbidity, escalation of costs and mortality risk. Severe neutropenia and FN episodes are also major drivers of CT dose delays and dose reductions, which have been shown to compromise survival outcomes in various curative settings [6].

Although the rate of breast cancer has increased in recent decades, patient survival has improved largely as a result of effective CT regimens, especially the widespread use of taxanes, such as docetaxel. However, many of the CT regimens that improve patient survival are associated with myelosuppression, which can lead to the development of adverse events, notably neutropenia. Neutropenia typically

Table4: ECOG Performance Status

		Total	No FN, n/N (%)	Developed FN, n/N (%)
ECOG Performance Status	0	11	11/66 (16.66)	0
	1	41	34/66 (51.51)	7/66 (10.60)
	2	14	14/66 (21.21)	0
Total		66	7/66 (10.60)	59/66 (89.39)

N = Total number of patients; n = number of patients; %= percentage, FN = febrile neutropenia

Table 5: Risk of Febrile Neutropenia

		Total	No FN, n/N (%)	Developed FN, n/N (%)
Risk of FN	Risk of FN < 20%	31	28/66 (42.42)	3/66 (4.54)
	Risk of FN ≥20%	35	31/66 (46.96)	4/66 (6.06)
Total		66	59/66 (89.39)	7/66 (10.601)

N = Total number of patients; n = number of patients; %= percentage, FN = febrile neutropenia

results in fever-like symptoms and increases performance status, suggesting some other

Table 6: Chemotherapy Regimen Protocol

		Total	No FN, n/N (%)	Developed FN, n/N (%)
Chemotherapy Regimen Protocol	TAC	27	23/66 (34.84)	4/66 (6.06)
	FEC	19	19/66 (28.78)	0
	AC + T	10	8/66 (12.12)	2/66 (3.03)
	CMF	10	9/66 (13.63)	1/66 (1.51)
Total		66	59/66 (89.39)	7/66 (10.60)

N = Total number of patients; n = number of patients; %= percentage, FN = febrile neutropenia; TAC= Docetaxel+Adriamycin+cyclophosphamide;FEC=5-fluorouracil+epirubicin+cyclophosphamide;AC+T= Adriamycin+cyclophosphamide+paclitaxol; CMF= cyclophosphamide+Methotrexate+5-fluorouracil

patient's susceptibility to the development of severe infections, which can be life threatening [8].Prophylaxis with recombinant G-CSF reduces the severity and duration of CT-induced neutropenia and the consequent risk of FN and is playing an increasingly broad role in supporting the delivery of myelosuppressive CT[6].

The mean age of patients in the study was 48.77±9.69 years in accordance with the study of Wani SQ *et al* [1]. The risk of FN increases with older age among the cancer patients on CT [9].Advanced age is also a predisposing factor for the development of FN [9,10].Similarly, majority of the patients in our study were in the 5th and 6th decade.

Advanced stage of cancer at diagnosis and especially those with bone marrow infiltration was predictive factors for FN [9, 10, and 11]. Similarly, our patients in advanced stage beyond stage II b were having FN.

The poor performance status is a predictor for FN [9, 11, and 12]. However, our study was not showing the correlation of FN with the correlates for its predisposition.

The predisposing factors associated with FN in our study did not show any correlation among our patients, which is contrary to the literature evidence. In our study, about the ECOG performance status, none of the patients in ECOG Performance Status of zero and two (total of 11 with zero and 14 with PS of two) developed FN, and patients with ECOG Performance Status of one were 41 patients, and seven developed FN. However, the various studies favor the correlation of low PS and FN [9].

The world literature suggests the following predisposing factors associated with the risk of FN like age > 60 years, poor performance score, previous episode of FN, previous hospitalization [6].

Regarding the risk of FN, number of patients having a risk of FN of < 20% were 29, out of which three developed FN despite G-CSF as secondary prophylaxis and those with risk of FN ≥ 20% were 37,out of which, four developed FN despite G-CSF as primary prophylaxis.

The main objective of managing breast cancer is to make the patients follow the treatment

with curative intent and avoid unnecessary delays as such, to have the optimum outcome of CT. However, various CT regimens are highly effective but not without adverse outcomes like FN. Our intention of providing G-CSF support in patients undergoing various chemotherapeutic protocols with curative intent might help such patients of continuing CT protocols. Various studies suggest that patients on CT with myelosuppressive potential might develop the FN [5].In our study, 7 patients out of 66 developed FN (10.6%), four out of 27 on TAC regimen developed FN (6.06%).Among ten patients on AC+T protocol two patients developed FN (3.03%), out of ten patients on CMF protocol, one developed FN (1.51%). Of 19 patients on FEC protocol, none developed FN. Out of seven patients only 1 patient developed grade 4 FN and 6 patients developed grade 3 FN without fever, and the duration of hospital stay of the patient with grade 4 FN was less than a week. Hence, this study revealed that the incidence of FN was only 10.6% in patients on G-CSF prophylaxis, when the world literature shows incidence can vary from 10 to 50% without G-CSF support depending on the chemotherapeutic regimen received by the patient.

Hence our study justifies the role of G-CSF prophylaxis (primary as well as secondary prophylaxis),so that patients complete their chemotherapy protocols within the prescribed period of time, and at the same time protect the patients from the morbidity and mortality associated with FN, and unwanted hospitalization and cost associated with its management.Multiple randomized trials have well established role of G-CSF in the prevention of FN. However other factors need to be identified responsible for predisposition of FN in patients on various myelosuppressive CT protocols.

Conclusion

The G-CSF prophylaxis helps the patients to follow their scheduled chemotherapy protocols, besides reduces the morbidity and mortality associated, and subsequent unwanted hospitalization and costs.

Authors' Contribution

SQW conceptualized, collected the data and wrote the initial manuscript.
TK did analysis, wrote the final manuscript and did proof reading.
MML did final corrections and proof reading.
All authors approved the final corrected manuscript.

Conflict of Interests

None

Ethical Considerations

Ethical committee approval was obtained for this study the copy of ethical approval is available with authors.

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