Original Article

# Impact of Granulocyte-Colony Stimulating Factor on Neutropenia and Quality of Life in Breast Cancer Patients Receiving Chemotherapy- An Observational Study

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## Abstract

Background & objectives: Breast cancer is the most common cancer among females in India. Adjuvant chemotherapy regimen can cause physical and psychological distress. Chemotherapy drugs have narrow therapeutic index and cause many ADRs like neutropenia which affects the quality of life. This study assessed the effect of Granulocyte -Colony Stimulating Factors (G-CSFs) on neutropenia and quality of life in breast cancer patients.

Methods: Pre-menopausal women with confirmed diagnosis of breast cancer, who have received adjuvant TAC chemotherapy regimen for 6-12 cycles were analyzed. The patients were divided in 2 groups, one group received chemotherapy only and the other received GCSF with chemotherapy. Quality of life (QOL) and incidence of febrile neutropenia (FN) in patients receiving chemotherapy were observed in each group. Assessment of QOL was done using QOL instrument of City of Hope National Medical Centre and Beckman Research Institute which is a questionnaire of 46-item ordinal scale that represents the four domains of quality of life including physical, psychological, social and spiritual well-being.

Results: 80 patients were evaluated, out of which 40 patients received chemo + GCSF (186 cycles) and 40 patients received only chemo (172 cycles). Incidence of febrile neutropenia was seen in 4.8% and 14.5% patients receiving chemo + GCSFs and only chemo respectively. While assessing QOL, the physical domain (specifically fatigue & insomnia) was most commonly affected among other domains.

Interpretations & conclusions: The use of primary GCSF was associated with reduced incidence of febrile neutropenia, anemia and other symptoms related to chemotherapy in patients having adjuvant TAC regimen.

**Keywords:** breast cancer, GCSF, febrile neutropenia, quality of life

## INTRODUCTION

Breast cancer is the most common cancer witnessed among Indian females, with age adjusted rate as high as 25.8 per 100,000 women and mortality rate 12.7 per 100,000 women.(1) Adjuvant TAC chemotherapy regimen [docetaxel (Taxotere), doxorubicin hydrochloride (Adriamycin) and cyclophosphamide] used for breast cancer can cause physical and psychological distress.(2)

Docetaxel containing regimen has been used widely. They have a slim therapeutic index and target not only the cancerous but fast-growing healthy cells as well. Chemotherapy induced ADRs like CINV (chemotherapy induced nausea and vomiting), CIN (chemotherapy induced neutropenia), anaemia, thrombocytopenia are prime leading distress factors in patients. Some other ADRs like alopecia, loss of weight and appetite, insomnia and pain, play an important role in affecting quality of life throughout the chemotherapy period.

CIN, anaemia, thrombocytopenia are the most common haematological toxicities(3,4) and important limiting factors in spacing of chemotherapy cycles which also leads to serious morbidity, increase hospitalisations and complications.(5–7)

Granulocyte colony-stimulating factors (G-CSFs) are additional growth factor supports that help in reducing the incidence of febrile neutropenia (FN).(8) Filgrastim is a human G-CSF and pegfilgrastim has polyethylene glycol (PEG) unit attached to it, both of which are used most commonly to treat CIN. G-CSF are widely used as primary as well as secondary

prophylaxis to prevent neutropenia induced complications. G-CSFs and other prophylactic antibiotics are used concomitantly to prevent febrile neutropenia (FN) during chemotherapy with docetaxel, adriamycin, and cyclophosphamide (TAC).[9]

Breast cancer and chemotherapy can affect the patient physically, physiologically and psychologically and it can manifest as depression, pain, anxiety and decreased social interaction. The quality of life related to health (Health Related Quality of Life - HRQoL) was a consequence of the realisation that good health is inevitable for good quality of life.[10]

The Quality-of-Life Instrument: CANCER PATIENT/CANCER SURVIVOR VERSION (COH-QOL) is a 46 item ordinal scale that evaluates the Quality of Life of a cancer survivor[11]. The QOL Breast Cancer instrument is based on previous versions of the QOL instrument developed by the researchers at the City of Hope National Medical Centre. The revised instrument embodied 46 items that reflected upon all four domains of quality of life namely physical, psychological, social and spiritual well-being.

The physical domain not only includes the patient's physical but also physiological well-being (e.g. fatigue, loss of appetite, pain, insomnia, constipation, nausea). It rates the overall physical health during chemotherapy. The emotional component encompasses the psychological domain, which includes both positive as well as negative mood indicators such as anxiety, depression and the limitations they ultimately lead to. Sexual quality of life indicates one's perception of sexual functions and changes affiliated to one's body. The social domain embraces the role of people around us and their support towards an individual and its disease. All these domains are interconnected.

The present study aimed to examine the effect of G-CSFs on quality of life of breast cancer survivors.

## MATERIAL AND METHODS

This study was done in the Department of Pharmacology, SCB Medical College & Hospital, Cuttack in collaboration with the Department of Medical Oncology of Acharya Harihar Postgraduate Institute of Cancer (AHRCC), the largest regional cancer center in Odisha.
The protocol was submitted and approved by both Institutional Ethics Committee (IEC) of SCB Medical College & Hospital and AHRCC Ethics committee prior to the commencement of the study.

Pre-menopausal women aged 18 to 60 years, with confirmed histopathological diagnosis of Stage IIa & IIb breast cancer by Department of Onco-pathology AHRCC and classified according to AJCC manual, 6$^{th}$ edition were enrolled in the study and those who received adjuvant TAC (docetaxel + doxorubicin + cyclophosphamide) chemotherapy regimen every 21 days for 6-12 cycles were included in the study. Recombinant G-CSFs - Filgrastim (300 mcg) for three days and Pegfilgrastim (6 mg) single dose were administered subcutaneously on the second day of chemotherapy i.e. between 24-48 hours after each cycle. Pregnant women, breast cancer patients on concomitant radiotherapy or with incomplete chemotherapy cycles, secondary malignancies, history of bone marrow or stem cell transplantation were excluded from the study.

Written informed consent was taken from the head of the corresponding departments before commencing the study as well as from the patients fulfilling the eligibility criteria if they were willing to participate. The study participants were explained about the purpose of study and how it will affect the quality of life.

Data of patients satisfying the inclusion and exclusion criteria, who were willing to be a part of the study were collected on a pre-designed case record form (CRF) by study group. Demographic variables including age, weight, body surface area (BSA) were recorded. The entire treatment protocol of the patient was noted thoroughly- the chemotherapy regimen and the duration of each cycle was noted. Consumption of G-CSFs during cycle and hospitalization stay were noted. Patients who received G-CSFs and those who had not received G-CSFs were categorized into 2 groups accordingly. Laboratory investigations i.e. DC, TLC, TPC, Hb before & after each chemotherapy cycle were checked. Physical examination was done and parameters such as body temperature, blood pressure, pulse rate, presence of pallor or icterus etc. were recorded on daily basis during their stay to observe patient status in each cycle. ANC (Absolute Neutrophil Count), Incidence of febrile neutropenia, Median Duration of Hospitalization (MDH) were observed in each cycle in both groups of patients.

The treatment protocol and chemotherapy regimen were in accordance to National Comprehensive Cancer Network (NCCN) guidelines.[12] Rate of neutropenia was assessed and prophylactic antibiotics and other medications were given as per Common Terminology Criteria for Adverse Events (CTCAEV 4.0) guidelines.[13]

Incidence of Febrile Neutropenia (FN) and its impact on quality of life were observed in each group i.e. those receiving G-CSF and not receiving any G-CSF. Assessment of QOL was done using QOL instrument of City of Hope National Medical Centre and Beckman Research Institute. It is a questionnaire comprising of 46 items arranged in an ordinal scale that evaluates the Quality of Life of a breast cancer survivor. The 46 elements represent physical, psychological, social and spiritual well-being, the four domains that determine the quality of life. Physical domain contains 8 scale of

symptoms: fatigue, change in appetite, aches/pain, changes in pattern of sleep, weight gain if any, vaginal dryness, menstrual fertility.
Interview technique was used by the investigator to gather the data and the questionnaire was filled out with the help of a nursing staff during the patient's interview. Alternatively, the patients were asked to fill the questionnaire under the supervision of a nursing staff wherein they were asked to encircle a number that represented the degree to which he/she agrees or disagrees with the statement according to the word anchors at the end of each scale.

The scoring system was built on a scale of 0 through 10, 0 representing the worst outcome possible and 10 representing the best. Some items had reverse anchors and so while coding those items, the scores were reversed accordingly. For example, if a subject encircles "3" on such an item, (10-3=7) then the score was recorded as a score of 7. The items with reverse anchors were: 1-7, 9, 10, 17-29, 31, 33-39 & 43. Thereafter, for analysis subscales were created by adding all of the items within a subscale and then creating a mean score.

The data was observed and entered in specially designed case record form. Information was entered on Microsoft excel 2010 spreadsheet and analyzed. All descriptive statistical analyses were accomplished using the Statistical Program for Social Sciences (SPSS v. 18.0). Categorical variables were represented as frequency & proportion. Analysis of the questionnaire was performed in accordance to the guidelines set up for determining the quality of life in breast cancer patients using the QOL instrument assembled by researchers at the City of Hope National Medical Center. Depending on the nature of the variable, the parameters were represented as frequency, percentage, measures of central tendency such as mean, median, and measures of deviation such as standard deviation (Confidence Interval) and range. Tests were performed with a significance level of $p<0.05$ using Friedman test.

## RESULTS

A total of 150 patients were screened, out of which data of 80 patients were taken into evaluation. The mean age, mean weight and mean BSA of the patients were found to be 44.6±1.0 years, 55.4±8.6 kg and 1.47±0.1$m^2$ respectively at baseline. Most of the patients (60%) belonged to T1 stage. As much as 48% of patients had moderately differentiated cancer with a score of 7 in accordance to Bloom Richardson Scoring system. The mean BR score was 6.6±0.77.

**Table 1** summarises the clinical characteristics of the patients. As evident from **Table 2**, there were 40 patients each in group 1 i.e. those receiving chemotherapy + GCSF and group 2 i.e. those receiving chemotherapy only. Total number of chemotherapy cycles received were 186 and 172 in group 1 and group 2, respectively. Incidence of febrile neutropenia was 4.8% and 14.5% in group 1 and group 2, respectively. The incidence of febrile neutropenia was significantly higher in group 2 patients (p=0.0002). Severe anaemia was seen in 5% and 12% in group 1 and group 2, respectively. Mean duration of hospitalisation which was 3 days/cycle in chemo + GCSFs group and 5 days/cycle in chemo only group, was evidently lower in the group 1, but not significant statistically. All patients completed the scheduled treatment.

## QUALITY OF LIFE SCORE

On assessing the QOL by the COH-QOL questionnaire, the physical domain was discovered to be primarily impacted in in group 2 patients i.e. chemotherapy only group, which was statistically significant ($p<0.0001$). Chemotherapy had a greater impact on the quality of life in the chemotherapy only group (group 2) as compared to patients receiving GCSF (group 1). Patients of group 2 most commonly suffered from fatigue and insomnia which was a statistically significant finding ($p<0.0001$).

| Parameter | Value |
|---|---|
| **Age (mean±SD) in years** | 44.6±1.0 |
| **weight (mean±SD) in kgs** | 55.4±8.6 |
| **BSA ($m^2$)** | 1.47±0.15 |
| **BR Score** | 6.6±0.77 |
| **HISTOLOGY** | |
| DUCTAL CARCINOMA | 53 |
| LOBULAR CARCINOMA | 27 |
| **tumor size** | |
| t0 | 17 |
| t1 | 48 |
| t2 | 8 |
| t3 | 5 |
| **lymph node involvement** | |
| n0 | 36 |
| n1 | 44 |
| **HORMONE RECEPTOR** | |
| ER/PR positive | 7 |
| triple negative | 16 |
| triple +ve | 24 |
| **her-2** | |
| positive | 29 |
| negative | 4 |

**Table 1.** Baseline characteristics of patients with breast cancer at diagnosis (n=80)

| VARIABLE | CHEMO + GCSF | CHEMO ONLY | p-value |
|---|---|---|---|
| **Number of patients** | 40 | 40 | |
| **Cycles** | 186 | 172 | |
| **Febrile neutropenia** | 9 (4.8%) | 25 (14.5%) | **0.0002#** |
| **MDH* (days/cycle)** | 3 (34%) | 5 (46%) | 0.17 |
| **Anaemia** | 46(24.7%) | 59 (34.3%) | 0.04# |
| **Grade 2** | 41(22%) | 47(33%) | 0.25# |
| **Grade 3** | 5(2.6%) | 12(6%) | 0.06# |
| **Thrombocytopenia** | 7 (2.6%) | 12 (4.6%) | 0.18# |

**Table 2.** Incidence of febrile neutropenia and other chemotherapy related events in course of the treatment *MDH- Mean Duration of Hospitalisation # Chi-square test

| DOMAIN | QOLQ C46 SCORE CHEMO + GCSF | | QOLQ C46 SCORE CHEMO ONLY | | p-value$ |
|---|---|---|---|---|---|
| | MEAN (SD) | MEDIAN (RANGE) | MEAN(SD) | MEDIAN (RANGE) | |
| **Physical well being** | 73(2.5) | 73(68-78) | 53(8.6) | 54(36-64) | **<0.0001** |
| **Psychological well being** | 157(11.6) | 157 (140-176) | 138(15.0) | 137(106-164) | 0.31 |
| **Social well being** | 68(7.4) | 68(58-82) | 72(9.4) | 76(52-87) | **0.04** |
| **Spiritual well being** | 32(4.6) | 33(24-39) | 32(6.8) | 32(19-43) | 1.0 |

**Table 3.** Quality of life score in patients after 6 cycles $ unpaired student t test

| OUTCOME | CHEMO + GCSF | | CHEMO ONLY | | p-value$ |
|---|---|---|---|---|---|
| | MEAN (SD) | MEDIAN (RANGE = 1-10) | MEAN (SD) | MEDIAN (RANGE = 1-10) | |
| **Fatigue** | 7.7(0.8) | 8 | 4.5(2.7) | 3 | **<0.0001** |
| **Loss of appetite** | 5.9(1.3) | 6 | 5.8(1.9) | 6 | 0.8 |
| **Pain** | 7.4(0.7) | 7 | 5.3(1.5) | 6 | **<0.0001** |
| **Insomnia** | 5.1(0.8) | 5 | 4.2(1.6) | 4 | 0.0021 |
| **Cancer chemotherapy (Distress)** | 4.5(1.1) | 5 | 4.2(0.8) | 4 | 0.17 |
| **Depression** | 6.8(1.9) | 7 | 4.9(2.6) | 4 | 0.0004 |

**Table 4.** Mean outcomes in patients of the two groups $ unpaired student t test

## DISCUSSION

The present study revealed that incidence of febrile neutropenia was seen most commonly in patients having adjuvant TAC chemotherapy. Pegfilgrastim, a long-acting GCSF was useful in decreasing the occurrence of febrile neutropenia and other related complications. According to the guidelines, the use of GCSF should be recommended right from the first cycle of chemotherapy regimens that are associated with ≥ 40% risk of febrile neutropenia.[14] The concomitant use of GCSF from the first cycle of chemotherapy as such reduces the frequency of febrile neutropenia in patients treated with TAC.[15] The mean age of patients in this study was 44.6 years as compared to 49.2 years in a study by Lee et al.[16]

In this study 80 patients were evaluated out of which 40 patients received only chemotherapy while other 40 received GCSF with chemo. 186 cycles in chemo + GCSF group and 172 cycles in chemo only group were analysed. The incidence of FN in the cycles having chemotherapy + GCSF was lower as compared to patients having chemotherapy only (4.8% vs 14.5%). This was in line with a former review of TAC regimen by Lee et al showing (16.4% vs 63.4%) FN.[16] In another study, the incidence of FN during TAC chemotherapy without any GCSF was found to be as high as 96.6% and it was merely 3.4% when pegfilgrastim was administered concomitantly with the chemotherapy cycles.[17] According to another study by Vogel et al. the use of GCSF for single agent docetaxel was associated with fewer incidences of febrile neutropenia in 20% of patients.[18]

Mean duration of hospitalisation per cycle, occurrence of anaemia and thrombocytopenia were less in patients receiving GCSF. In the present study, the mean duration of hospitalisation was 3 days/cycle in chemo + GCSF group and 5 days/cycle in chemo only group. In study by A. minisini et al[19], the median number of duration of hospitalisation was 5. Grade 2 anaemia and severe anaemia were seen in 22% & 2.6% out of 186 cycles in chemo + GCSF group. Subsequently, in chemo only group, grade 2 anaemia and severe anaemia were higher i.e. 33% & 6% out of 170 cycles. Severe anaemia was seen in 3% out of 335 cycles with 8 cycles (2.2%) needing blood transfusion in Lee et. al study.[16] In a study by Martin et. al, there was a reduction of grade 2 anaemia to grade 4 as well as reduction in transfusional requirements associated with use of PPG (Primary Prophylaxis with GCSF).[15] Patients undergoing chemotherapy and those with chemotherapy induced neutropenia and anaemia may encounter shortfalls in QOL on several grounds. They are more susceptible to infections, need extra precautions and regular monitoring. Patients suffering from FN need long duration

of hospitalisation and antibiotics.[20]

A QOL questionnaire is a useful tool to pin down, prioritize, and construct strategies for apt treatment of any cancer. They can also help in improving the patients' reported symptoms and palliative care. The purpose of using QOL tools is to revamp the treatment strategies and pivot on patient care rather than disease. The QOL Breast Cancer instrument formulated by City of Hope National Medical center is an amended validated instrument made up of 46 items that represent physical, psychological, social and spiritual domain of one's well-being. The health conditions and bodily functions were superior in patients receiving GCSF. Patients receiving GCSF fared better than patients who didn't receive GCSF in terms of physical and psychological well-being. Altogether, GCSF have a superior pay-off on quality of life of cancer patients.

Quality of life measured by QOLQ C46 score shows mean physical well-being score to be 73±2.5 in chemo + GCSF group and 53±8.6 in chemo only group. In Lee at al study[16], mean physical well-being score was 14.6±21.5 where QOL was measured by FACT-B while in a study by Gavric et al when women with breast cancer were assessed by QOLQ C30 score, the mean physical functioning score was 66.32±17.82.[21] The psychological well-being score was 157 in chemo + GCSF group and 138 in patients having only chemotherapy. In the study by Gavric et al, the role functioning score was 46±20.88.[21] Similarly the social well-being score was 68 in chemo + G-CSF group, 72 in chemo group in our study and 37±27.58 in Gavric et al study.[21]

In this study, the lowest mean value score was for symptom scale insomnia followed by pain and fatigue. Lesser value of score for symptom scale indicates that, the symptom is more distressing to patients as per QOL questionnaire. This finding was similar to Gokgoz et al study, where the most affected symptoms were fatigue, financial difficulties, insomnia and pain. Primary Pegfilgrastim (PPG) was associated with reduction in anorexia (5.9±1.29), fatigue (7.7±0.8), myalgia/pain (7.4±0.7), insomnia (5.1±0.8), depression (6.8±1.9). In study by Martin et al. PPG was associated with statistically significant curtailment of occurrence of asthenia, anorexia, myalgia, nail disorders in patients treated with TAC regimen.[15] The decline in the HRQoL during treatment was a consequence of the adverse events associated with chemotherapy and cancer itself but this is less eventful in patients with PPG.[20] In this study patients receiving GCSF with chemotherapy suffered from depression and social concern less as compared to patients receiving chemotherapy alone. In a study by Mary E et al[22] asthenia (5.6%), stomatitis (23.2%), diarrhoea (2.7%), myalgia (0.2%) were less in TAC+GCSF group as compared to TAC alone group. Breast cancer itself and chemotherapy associated with it impacted considerably on physical condition, family and social life of women in control group as compared to GCSF group. Mean values of score were lower in GCSF group which was also found in subsequent studies.

To conclude, primary prophylaxis with GCSF positively correlated with reduced incidence of febrile neutropenia, anaemia and other symptoms related to chemotherapy in breast cancer patients having adjuvant TAC regimen. The combination of GCSF with chemotherapy should be considered from the start, which can significantly enhance the quality of life of breast cancer survivors.

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