Open Access

Original Article

Neutropenia: Frequency and Management Outcomes in Women with Breast Cancer Receiving Anthracycline Based Chemotherapy

Tahir Manzoor Lone, Muhammad Nadeem, Amjad Khan, Muhammad Umair, Misbah Hamid*, Masaba Masood

Department of Medical Oncology, Combined Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan
*Department of Family Medicine, National Health Service United Kingdom

ABSTRACT

Objective: To analyse the frequency and management outcome of Neutropenia in women with breast cancer receiving Anthracycline chemotherapy.

Study Design: Comparative Cross-sectional study.

Place and Duration of Study: Oncology Department, Combined Military Hospital, Rawalpindi Pakistan, from Feb to Nov 2021.

Methodology: This study was conducted on 200 patients who have breast cancer who were put on an Anthracycline-based chemotherapy regimen. They underwent three or four cycles of chemotherapy as per the treatment plan. A complete blood picture was carried out on all patients after the cycle, and Neutropenia was graded according to the National Cancer Institute's Common Toxicity Criteria. Grade III and IV neutropenia patients were administered Granulocyte colony-stimulating factor and the response was observed.

Results: A total of 200 patients with breast cancer receiving Anthracycline-based chemotherapy were included. The mean age of the patients was 54.775±9.649 years. Seven hundred sixty-two cycles were recorded on these patients during the study period. Of these 762 cycles, 245(32.1%) episodes of Neutropenia were recorded. 60(24.4%) had either Grade III or IV neutropenia. Out of those having Grade III or IV neutropenia, 50(83.3%) had improvement after administration of G-CSF, while 10(16.7%) did not show any improvement. The advancing age of patients had a statistically significant relationship (*p*-value-0.001) with poor response to G-CSF treatment in our study participants.

Conclusion: Considerable number of post-menopausal patients with advanced breast cancer taking Anthracycline-based chemotherapy showed the presence of Neutropenia. G-CSF emerged as an effective treatment for high-grade Neutropenia in these patients.

Keywords: Anthracycline, Breast cancer; Granulocyte colony-stimulating factor, Neutropenia.

How to Cite This Article: *Lone TM, Nadeem M, Khan A, Umair M, Hamid M, Masood M. Neutropenia: Frequency and Management Outcomes in Women with Breast Cancer receiving Anthracycline based Chemotherapy. Pak Armed Forces Med J 2024; 74(4): 901-905. DOI: https://doi.org/10.51253/pafmj.v74i4.7770*

INTRODUCTION

Neoplastic conditions have been prevalent in all parts of the world, absorbing much of the healthcare budgets of developed and developing countries.[1] One of the significant causes of mortality and morbidity in women across the globe is carcinoma of the breast.[2] Number of factors at the time of diagnosis determine the short-term and long-term prognosis in patients who have breast cancer.[3] Depending upon the stage and hormonal profile of the disease, physicians devise a strategy right from the start and aggressive management of this life-threatening illness may prone the patient towards multiple adverse effects.[4]

Various treatment modalities have been in clinical practice for patients with breast cancer. The advanced disease usually requires a combination of chemotherapy and surgical resection with an aggressive approach to reducing the chances of mortality and better outcomes.[5] Management modalities, especially chemotherapeutic agents offered for advanced breast cancer, are associated with several side effects, including haematological side effects.[6]

Various haematological adverse effects, including Neutropenia, have been seen in a significant number of breast cancer patients using Anthracycline-based regimens. Ma *et al*. studied patients with invasive breast cancer and looked for Neutropenia after the first cycle of chemotherapy. They highlighted that Neutropenia is a common finding in patients undergoing chemotherapy from advanced breast cancer and is usually associated with poor outcomes if it occurs in the first cycle and is left untreated.[7] Kim *et al*. conducted the study from Korea regarding the incidence and predictors of febrile Neutropenia

Correspondence: Dr Tahir Manzoor Lone, Department of Oncology, Combined Military Hospital, Rawalpindi Pakistan
Received: 06 Dec 2021; revision received: 15 Jan 2022; accepted: 20 Jan 2022

among early-stage breast cancer patients receiving Anthracycline-based chemotherapy. They concluded that around 44% of patients had Grade IV Neutropenia, and a considerable number of patients had treatment delays.[8] Bennet *et al*. in 2014 studied Colony-Stimulating Factors for febrile Neutropenia during cancer therapy. They revealed that though guidelines may vary worldwide for using G-CSF for Neutropenia in cancer patients, their use still has auspicious results.[9]

Weighing the risks and benefits of treatment options for malignant conditions like breast cancer has been the primary role of the treating team. Clinicians worldwide have different opinions regarding the efficacy and safety profile of G-CSF used for the treatment or prophylaxis of chemotherapy-induced Neutropenia in cancer treatment. Siddiqui *et al*. recommended that the use of G-CSF may not confer significant benefits to patients with uncomplicated febrile Neutropenia and should be reserved for complicated cases where the expected risk of infection is high and the duration of Neutropenia is prolonged, or for patients with documented infections that are refractory to antibiotic treatment.[10] Limited local data is available regarding the role of G-CSF in chemotherapy-induced Neutropenia in patients with breast cancer. We planned this study with the rationale to look for neutropenia and management outcome of Neutropenia in women with breast cancer receiving Anthracyclines chemotherapy

METHODOLOGY

The comparative cross-sectional study was conducted at the Oncology Department of Combined Military Hospital, Rawalpindi Pakistan, from February to November 2021. Ethical approval (via letter number 217/11/21) was taken from the Ethical Review Board Committee. The sample size was calculated using the WHO sample size calculator, using the population proportion of chemotherapy-induced Neutropenia in breast cancer patients as 31.9%.[11]

Inclusion Criteria: All female patients aged 18 to 65 years having breast cancer and put on Anthracycline-based chemotherapy were included.

Exclusion Criteria: Patients with metastatic or primary neoplastic disease other than breast, patients with low neutrophil count before chemotherapy, patients with known hematopoietic disorder in addition to breast cancer or those using medications other than Anthracycline, which were associated with Neutropenia, patients who had any contraindication to the use of G-CSF or those who refused the use of G-CSF were excluded.

The sample was gathered by using the non-probability consecutive sampling technique. After written informed consent from the participants, patients presenting with breast cancer were put on Anthracycline-based chemotherapeutic regimens and the inclusion and exclusion were included in the study. Diagnosis of breast cancer was made by a consultant oncologist based on clinical, radiological and pathological criteria.[12] Anthracycline-based chemotherapy included regimens based on any of Doxorubicin (AC) and Epirubicin (EC, FEC).[13] Neutropenia was assessed on blood complete picture done after each cycle on day 7, day 10 and day 14. Neutropenia, if observed, was divided into four grades according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC). Grade-1 equates to a neutrophil count of between 1.5 and 2.0×109/L; Grade 2 equates to a neutrophil count of between 1.0 and 1.5×10^9/L; Grade 3 equates to a neutrophil count of between 0.5 and 1.0×10^9/L; and Grade 4 equates to a neutrophil count below 0.5×10^9/L.14 G-CSF was given to all the patients with Grade III or Grade IV Neutropenia in a dose of 300 micrograms/kg for three consecutive days.[15] Blood complete picture was repeated on day 10th of the assessment of neutrophil count. Improvement in neutrophil count was defined as average neutrophil count or reduction in severity grade.

All statistical analysis was performed using the Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Mean and standard deviation were calculated for the patients' ages. Frequency and percentages were calculated for the qualitative variables. The Pearson Chi-square test was applied to look for the association of various factors with improvement in neutrophil count after G-CSF administration. The *p*-values were considered significant in the analysis if they were less than or equal to 0.05.

RESULTS

A total of 200 patients with breast cancer receiving various Anthracycline based chemotherapy regimens were included in the final analysis. The mean age of the patients was 54.775±9.649 years. Seven hundred sixty-two cycles were recorded on these patients during the study period. Of these 762 cycles, 245(32.1%) episodes of Neutropenia of any

grade were recorded (Table-I). Of the 245 episodes of Neutropenia observed, 99(40.4%) were grade I, 86(35.1%) were Grade II, 42(17.1%) were Grade III and 18(7.3%) were grade IV neutropenia. Grade III /IV neutropenia was most commonly observed with the first cycle of chemotherapy, and out of those having Grade III or IV neutropenia, 50(83.3%) had improvement after administration of G-CSF. In comparison, 10(16.7%) did not show any improvement. It was revealed that the advancing age of patients had a statistically significant relationship (*p*-value-0.001) with poor response to G-CSF treatment in our study population (Table-II).

Table-I: Characteristics of Patients with Breast Cancer Receiving Anthracycline based Chemotherapy (n=200)

Study Parameters	n(%)
Age (years)	
Mean±SD	54.775±9.649 years
Range (min-max)	23 years-65 years
Total No. of cycles	762 cycles
Grades of Neutropenia	
Grade I	99(12.9%)
Grade II	86(11.3%)
Grade III	42(5.5%)
Grade IV	18(2.4%)
Grade III or IV Neutropenia in Chemotherapy Cycles	
Cycle I	23(38.3%)
Cycle II	20(33.3%)
Cycle III	10(16.7%)
Cycle IV	07(11.7%)
Response to G-CSF Treatment	
Improved	50(83.3%)
Not improved	10(16.7%)

Table II: Association of Various Factors with Response to G-CSF Treatment for Grade III or IV Neutropenia (n=200)

Factors	Good response to G-CSF	Poor response to G-CSF	*p*-value
Age			
<50 years	33(66%)	01(10%)	0.001
>50 years	17(34%)	09(90%)	
Grade of Neutropenia			
Grade III	36(72%)	06(60%)	0.459
Stage IV	14(28%)	04(40%)	
Cycle of Chemotherapy			
I and II	36(72%)	07(70%)	0.899
III and IV	14(28%)	03(30%)	
Presence of Comorbidities			
No	32(64%)	04(40%)	0.162
Yes	18(36%)	06(60%)	

DISCUSSION

Neoplastic conditions have been a challenge for physicians across the globe. The biological, psychological, and social dimensions of cancers test the patient and the treating team. The disease and treatment modalities prone the patient towards several associated health-related conditions that must be managed in time to save the patient from long-term disastrous consequences. Patients with advanced breast cancer managed with Anthracycline-based chemotherapeutic regimens face similar problems. Various systems of the body are affected during illness and treatment. We studied one adverse haematological effect in these patients and a response to treatment of that very adverse effect, i.e., Neutropenia.

Gadisa *et al*. conducted a study in 2020 regarding patterns of Anthracycline-based chemotherapy-induced adverse drug reactions and their impact on relative dose intensity among women with breast cancer in Ethiopia.[16] They concluded that Grade-III neutropenia was the most frequently reported adverse drug reaction among their study participants, and the response of Neutropenia to G-CSF was remarkable. Our results supported the results generated by Gadisa *et al*., and Grade III and IV neutropenia was a common finding in our patients, and the response of Neutropenia to G-CSF was more than 80%.

The impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving Docetaxel plus cyclophosphamide chemotherapy was studied by Chan *et al*. in 2011. They came up with the findings that routine administration of G-CSF was highly effective in reducing the rates of febrile Neutropenia in breast cancer patients receiving Docetaxel plus Cyclophosphamide chemotherapy.[17] Our study results were in line with their results. Though we did not study febrile Neutropenia, severe Neutropenia showed significant improvement with G-CSF in our study participants. Bongiovanni *et al*. studied the role of recombinant granulocyte colony-stimulating factor (rG-CSF) in the management of Neutropenia induced by anthracyclines and ifosfamide in patients with soft tissue sarcomas in 2017. They revealed that rG-CSF treatment was adequate for the management of severe Neutropenia and reduced the need for hospital admission among patients suffering from soft tissue sarcomas.[18] Our target population was different, but the dependent variable and agent studied were similar, and the results generated were similar.

A randomized multicenter phase II trial of mecapegfilgrastim single administration versus granulocyte colony-stimulating growth factor on

treating chemotherapy-induced Neutropenia in breast cancer patients was published by Wang *et al*. in 2019. It was concluded that both these options were equally effective in managing chemotherapy-induced Neutropenia in breast cancer patients.[19] Our target population was quite similar. However, our study design was our main limitation. We did not conduct a randomized controlled trial and generated results via a comparative cross-sectional study.

LIMITATIONS OF STUDY

Patients taking cytotoxic drugs are a high-risk group for haematological adverse effects, including Neutropenia. Our results do not conclude that Neutropenia was a direct effect of Anthracycline-based chemotherapy. This remains one of the main limitations of our study. Another limitation was the lack of a placebo group in our study.

CONCLUSION

A considerable number of post-menopausal patients with advanced breast cancer taking Anthracycline-based chemotherapy showed the presence of Neutropenia. G-CSF emerged as an effective treatment for high-grade Neutropenia in these patients.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

LTM & NM: Conception, study design, drafting the manuscript, approval of the final version to be published.

KA & UM: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

HM & MM: Data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021; 71(1): 7-33. https://doi.org/10.3322/caac.21654
2. Alkabban FM, Ferguson T. Breast Cancer. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
3. Lüftner D, Schneeweiss A, Hartkopf AD, Muller V, Wockel A, Janni W, et al. Update Breast Cancer 2020 Part 2 - Advanced Breast Cancer: New Treatments and Implementation of Therapies with Companion Diagnostics. Geburtshilfe Frauenheilkd 2020; 80(4):3 91-398. https://doi.org/10.1055/a-1111-8775
4. Maajani K, Jalali A, Alipour S, Khodadost M, Tohidinik HR, Yazdani K. The Global and Regional Survival Rate of Women With Breast Cancer: A Systematic Review and Meta-analysis. Clin Breast Cancer 2019; 19(3): 165-177. https://doi.org/10.1016/j.clbc.2019.01.006
5. PDQ Adult Treatment Editorial Board. Breast Cancer Treatment (Adult) (PDQ®): Patient Version. 2021. In: PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute (US); 2002.
6. Heery M, Farley S, Sparkman R, Healy J, Eighmy W, Zahrah G, et al. Precautions for Patients Taking Aromatase Inhibitors. J Adv Pract Oncol 2020; 11(2): 184-189. https://doi.org/10.6004/jadpro.2020.11.2.6
7. Ma RM, Chen CZ, Zhang W, You J, Huang DP, Guo GL. Prognostic Value of Chemotherapy-Induced Neutropenia at the First Cycle in Invasive Breast Cancer. Medicine 2016; 95(13): e3240. https://doi.org/10.1097/MD.0000000000003240
8. Kim HS, Lee SY, Kim JW, Choi YJ, Park IH, Lee KS. Incidence and Predictors of Febrile Neutropenia among Early-Stage Breast Cancer Patients Receiving Anthracycline-Based Chemotherapy in Korea. Oncology 2016; 91(3): 274-282.
9. Bennett CL, Djulbegovic B, Norris LB, Armitage JO. Colony-stimulating factors for febrile neutropenia during cancer therapy [published correction appears in N Engl J Med 2013; 369(3): 293. Dosage error in article text]. N Engl J Med 2013; 368(12): 1131-1139. https://doi.org/10.1056/NEJMct1210890
10. Siddiqui T, Burney IA, Kakepoto GN, Khurshid M, Salam A, Smego RA. Lack of benefit of Granulocyte Macrophage or Granulocyte Colony Stimulating Factor in Patients with Febrile Neutropenia. J Pak Med Assoc 2002; 52(5): 110-120.
11. Hellemond IEGV, Smorenburg CH, Peer PGM, Swinkels ACP, Seynaeve CM, van der Sangen MJC, et al. Assessment and management of bone health in women with early breast cancer receiving endocrine treatment in the DATA study. Int J Cancer 2019; 145(5): 1325-1333. https://doi.org/10.1002/ijc.32205
12. Nounou MI, ElAmrawy F, Ahmed N, Abdelraouf K, Goda S, Syed-Sha-Qhattal H. Breast Cancer: Conventional Diagnosis and Treatment Modalities and Recent Patents and Technologies. Breast Cancer 2015; 9(Suppl 2): 17-34. https://doi.org/10.4137/BCBCR.S29420
13. Shah AN, Gradishar WJ. Adjuvant Anthracyclines in Breast Cancer: What Is Their Role?. Oncologist 2018; 23(10): 1153-1161. https://doi.org/10.1634/theoncologist.2017-0672
14. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. Predictive value of chemotheraspy-induced neutropenia for the efficacy of oral fluoropyrimidine S-1 in advanced gastric carcinoma. Br J Cancer 2007; 97(1): 37-42. https://doi.org/10.1038/sj.bjc.6603831
15. Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in Neutropenia.J Immunol 2015; 195(4): 1341-1349. https://doi.org/10.4049/jimmunol.1500861
16. Gadisa DA, Assefa M, Tefera GM, Yimer G. Patterns of Anthracycline-Based Chemotherapy-Induced Adverse Drug Reactions and Their Impact on Relative Dose Intensity among Women with Breast Cancer in Ethiopia: A Prospective Observational Study. J Oncol 2020; 2020: 2636514. https://doi.org/10.1155/2020/2636514
17. Chan A, Fu WH, Shih V, Coyuco JC, Tan SH, Ng R. Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. Support Care Cancer 2011; 19 (4): 497-504. https://doi.org/10.1007/s00520-010-0843-8

18. Bongiovanni A, Monti M, Foca F, Recine F, Riva N, Di Iorio V, et al. Recombinant granulocyte colony-stimulating factor (rG-CSF) in the management of neutropenia induced by anthracyclines and ifosfamide in patients with soft tissue sarcomas (NEUSAR). Support Care Cancer 2017; 25(1): 111-117. https://doi.org/10.1007/s00520-016-3390-0

19. Wang T, Wu B, Hu X, Liu J, Zhang T, Li F, et al. A randomized multicenter phase II trial of mecapegfilgrastim single administration versus granulocyte colony-stimulating growth factor on treating chemotherapy-induced neutropenia in breast cancer patients. Ann Transl Med 2019; 7(9): 196. https://doi.org/10.21037/atm.2019.04.10