Original Article

Challenges in Assessing Nutritional Impact on White Blood Cell Count in Breast Cancer Patients Undergoing Chemotherapy: The Role of Filgrastim

Akhtar K,[1] Arefin S,[2] Khanam F,[3] Islam SN,[2] Begum N[4]

ABSTRACT

Background: One of the most frequent and serious adverse effects of chemotherapy for patients with breast cancer is myelo suppression, especially neutropenia. There have been suggestions for nutritional treatments to boost immunological function. However, evaluating their separate effects on white blood cell (WBC) recovery is made more difficult by the concurrent administration of Filgrastim. This study examines how nutrition affects WBC counts in patients undergoing chemotherapy who are on Filgrastim. **Methods:** This is a randomized, parallel-group clinical trial with 52 participants in each arm that includes adult women with newly diagnosed breast cancer who are recommended for chemotherapy at a cancer treatment day care center at the National Institute of Cancer Research and Hospital (NICRH), Dhaka. The results were measured using a semi-structured questionnaire that had been pretested. Since the only intervention group received three hen-boiled eggs (one entire and two only white parts) daily, one omega-3 fatty acid tablet, and one vitamin D tablet (2000 I U), no placebo was utilized in this trial due to ethical concerns and convenience. Machine SYSMEX XN 350, an automated cell counter, performed the hematology analysis. Blood samples were taken and brought to the lab while taking every aseptic care. Statistical study evaluated differences between and between groups while taking Filgrastim's impact into account. **Results:** There was a significant difference between the intervention and control groups ($p = 0.021$), with a small drop in the total WBC count in both groups. While neutrophil levels stayed constant, lymphocyte percentages fluctuated somewhat. In both groups, the percentage of monocytes increased significantly ($p = 0.003$, $p < 0.0001$). The intervention group's basophil percentage rose noticeably ($p = 0.031$). The results demonstrate how challenging it is to separate the pharmacologic effects of Filgrastim from the effects of diet. **Conclusion:** There is conflicting evidence on the impact of nutritional interventions on WBC recovery in chemotherapy patients receiving Filgrastim, despite the fact that they may enhance immune function. Future studies should look into study designs that more clearly differentiate pharmaceutical effects from nutritional contributions, as well as alternative immunological biomarkers besides WBC counts.

Key words: Nutritional intervention, WBC count, breast cancer, inj Filgrastim, chemotherapy

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Author's Affiliation

1. *Khursheda Akhtar, Associate Professor, Public Health and Hospital Administration, National Institute of Preventive and Social Medicine (NIPSOM)
2. Prof. Dr. Md. Saidul Arefin, Director, Institute of Nutrition and Food Science (INFS) University of Dhaka.
3. Fahmida Khanam, Associate Professor Virology, Dept of Microbiology and Mycology, National Institute of Preventive and Social Medicine (NIPSOM)
4. Prof. Sheikh Nazrul Islam, PhD, Ex-Director, Institute of Nutrition and Food Science (INFS), University of Dhaka
5. Prof. Dr. Nadia Begum, Prof. and Head Department of community Medicine and Public Health, ZH Sikder Women's Medical College and Hospital.

Address of Correspondence: *Dr. Khursheda Akhtar, Associate Professor,Public Health and Hospital Administration, National Institute of Preventive and Social Medicine (NIPSOM), Email: dr.khursheda1974@gmail.com, Contract No: 01714712174

Introduction

Chemotherapy is the mainstay of treatment for breast cancer, one of the most common cancers in the world. Chemotherapy can have adverse effects because it destroys bone marrow cells that make blood. This is called myelosuppression, and it causes thrombocytopenia (lower platelets), anemia (lower red blood cells), and neutropenia (lower neutrophils [white blood cells]). Hospitalization may be necessary for severe cases of neutropenia, which might raise the risk of infection. Anemia and neutropenia can both result in weariness, which patients frequently describe as the most taxing side effect of chemotherapy.[1] By giving immune cells enough nutrients in the right amounts, nutrition plays a crucial part in controlling the best possible immune response. Numerous macronutrients, including certain amino acids, cholesterol, and fatty acids, as well as a variety of micronutrients, including vitamins and minerals, have been shown to have a significant and targeted effect on healthy immunological function.[2] However, it is unclear how much nutritional therapies affect WBC recovery in clinical settings where granulocyte-colony stimulating agents (G-CSFs) like Filgrastim are frequently used to lessen chemotherapy-induced neutropenia.

Rich in critical amino acids, egg protein has been researched for its potential to improve immunological function and preserve muscle during illness.[3] By regulating cytokine production and lowering oxidative stress, omega-3 fatty acids—in particular, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—have anti-inflammatory qualities and may improve immune cell function.[4] In a similar vein, vitamin D is essential for immune modulation, impacting both innate and adaptive immune responses; deficits have been connected to poorer outcomes and heightened vulnerability to infections in cancer patients.[5] Few clinical studies have explicitly looked at how these nutrients affect WBC recovery in patients after chemotherapy, despite these potential advantages.

Oncologists frequently utilize filgrastim, a recombinant human G-CSF, to increase neutrophil production and shorten the duration of chemotherapy-induced neutropenia.[6] Its administration makes it more difficult to evaluate nutritional therapies that try to modulate hemopoiesis, even though it is helpful in restoring WBC numbers. WBC count recovery in Filgrastim-treated patients is mostly fueled by pharmaceutical stimulation rather than natural physiological reactions, which may obscure the benefits of dietary changes. According to a study, leukocyte overshoot was seen in 76.4% (42/55) of patients and 71.2% (84/118) of patients as a result of using Filgrastim. The highest white blood cell count of ≥30,000/mm^3 was recorded in 30.5% (36/118) of the patients and 45.5% (25/55) of the patients. It was recorded in 39.3% (33/84) of the patients on the first day following the administration of pegfilgrastim and 26.2% (22/84) on the second day.[7] Research on the evaluation of nutritional interventions in cancer patients receiving chemotherapy is expanding because of the possible influence of diet on immune function. However, assessing the separate effects of diet on WBC recovery is made extremely difficult by the extensive use of Filgrastim in clinical oncology. The necessity to draw attention to and resolve this methodological problem justifies this investigation. This study offers important insights into the limitations of WBC count as a main immunological measure in such therapeutic settings by examining WBC count dynamics in individuals receiving both dietary treatments and Filgrastim. The results also highlight how important it is to investigate different immunological indicators and improve research techniques in nutritional oncology. Filling in these gaps will help create more efficient and comprehensible research that evaluates the actual influence of diet on the outcomes of cancer patients.

The purpose of this study was to look at how WBC counts in patients with breast cancer receiving chemotherapy were affected by a nutritional intervention that included egg protein, omega-3 fatty acids, and vitamin D. But as part of their regular supportive treatment, all patients also received filgrastim, which probably had an impact on their WBC results. This study emphasizes the need for other immunological biomarkers beyond WBC count alone to assess nutritional impact in chemotherapy patients, even though there were no discernible differences in WBC counts between the intervention and control groups. This paper highlights the difficulties in evaluating dietary interventions in clinical cancer settings and offers suggestions for future research methodologies by examining the implications of Filgrastim's effect on haematologic recovery.

Methods

This randomized, parallel-group clinical trial included adult women with recently diagnosed

breast cancer receiving chemotherapy at NICRH, Dhaka. Exclusion criteria encompassed advanced-stage cancer, metastases, recurrence, extreme age (below 18 or above 50), and co-morbidities like diabetes, thyroid disease, vascular insufficiency, renal or liver disease, parathormone deficiency, high blood pressure, abnormal lipid profiles, mental illness, or use of drugs antagonistic to omega-3 fatty acids or vitamin D. The sample size, calculated based on WBC differences from a prior study[8] required 52 participants per group to achieve 80% power at a 0.05 alpha level. Data collection occurred from November 2022 to December 2023, with ethical clearance from BMRC, the University of Dhaka, and NICRH. Participants provided written consent per the Declaration of Helsinki. No placebo was used; the intervention group received three hen-boiled eggs daily, an omega-3 tablet, and a 2000 IU vitamin D tablet. Hematology analysis was conducted using the SYSMEX XN 350 automated cell counter, measuring hemoglobin, hematocrit, RBC, WBC, and platelets[9] Blood samples were collected, labeled, and transported in EDTA tubes under aseptic precautions to the NIPSOM lab, ensuring temperature control and quality assurance. Samples were processed using standard laboratory procedures, with calibration and quality control to maintain accuracy. Statistical analysis was conducted using SPSS version 27, employing a two-tailed test with a 95% confidence interval. The Shapiro-Wilk test assessed data normality, while the Kruskal-Wallis H test and Friedman Rank test evaluated differences across three time points. Findings contribute to understanding the hematological impact of nutritional and supplement interventions in chemotherapy patients.

Results

Table 1. Socio-demographic characteristics of the respondents

General characteristics	Case / Intervention group (n=52) n (%)	Control group (n=52) n (%)	P-value
Age (years) (Mean± SD)(Min-max)	(45.0±8.8) (26-60)	(45.7±8.3) (26-67)	P>0.05
≤40	20 (38.5)	21 (40.4)	
>40	32 (61.5)	31 (59.6)	
Education			
Illiterate	23 (44.3)	23 (44.3)	P>0.05
Up to class 5	19 (36.5)	20 (38.5)	
Secondary (SSC*) and above	10 (19.2)	09 (17.2)	
Occupation			
Employed	10 (19.2)	09 (17.2)	P>0.05
Housewives	42 (80.8)	43 (82.8)	
Family Income (BDT) (Mean± SD)	(18230±9394)	(15192±6237)	P>0.05
(Minimum-maximum)	(5000-50000)	(5000-30000)	
≤15000	29 (55.7)	32 (61.5)	
>15000	23 (44.3)	20 (38.5)	
Marital status			
Married	34 (65.5)	38 (73.1)	P>0.05
Widow/divorced/separated	18 (34.5)	14 (26.9)	
Living areas			
Dhaka	20 (38.5)	23 (44.5)	P>0.05
**Outside of Dhaka	32 (61.5)	29 (55.5)	
Smoking habit			
Yes	19 (36.5)	18 (34.5)	P>0.05
No	33 (63.5)	34 (65.5)	

*Only n=05 completed SSC for case and n=04 for control. **Chittagong, Barisal, Mymensingh, Sylhet, Khulna, and Rangpur

The sociodemographic and personal traits of breast cancer patients in the intervention and control groups were shown in table 1. There was no discernible change in the average age of the participants between the intervention and control groups, which were 45.0±8.8 and 45.7±8.3 years, respectively. 44.3% of participants in both groups lacked formal education. While fewer participants in the intervention group (19.2%) had completed secondary education or higher than those in the control group (17.2%), more individuals in the intervention group (36.5%) had education up to class 5, compared to 38.5% in the control group. Housewives made up the majority of participants in both groups (80.8% in the intervention group and 82.8% in the control group). Although the intervention group's average family income was higher (BDT 18,230±9,394) than the control group's (BDT 15,192±6,237), the difference was not statistically significant. Compared to 73.1% of individuals in the control group, 65.5% of participants in the intervention group were married. Compared to the control group (26.9%), a higher percentage of participants in the intervention group (34.5%) were widowed, divorced, or separated. Geographically, more individuals in the control group (44.5%) resided in Dhaka than in the intervention group (38.5%). Participants in the intervention group reported smoking at a rate of 36.5%, whereas those in the control group reported smoking at a rate of 34.5%. There were no statistically significant variations in the two groups' sociodemographic parameters overall.

Table 2: Changes of WBC of the Intervention and Control Groups across Three Timelines

Bio-chemical (across 3-timelines (Mean± SD)	***Baseline***	*Follow-up1*	*End line*	@p-values Within groups	**p-values Between groups Case Verses. Control**
	Total WBC count (TC) $10^3/\mu L$				
Intervention group (n=52)	9.7±10.5	7.8±3.6	7.7±4.6	$^{W}p=0.828$	$^{Base}p=0.412$ $^{Follow}p=0.818$ $^{End}p=0.844$
Control group (n=52)	8.4±2.5	7.1±4.3	7.5±7.2	$^{W*}p=0.021$	
	Lymphocytes (%)				
Intervention group (n=52)	22.7±8.8	19.1±11.4	20.1±11.7	$^{W}p^{*}=0.010$	$^{Base}p=0.941$ $^{Follow}p=0.210$ $^{End}p=0.682$
Control group (n=52)	22.6±7.6	23.8±16.5	20.8±12.5	$^{W}p=0.156$	
	Neutrophils (%)				
Intervention group (n=52)	71.0±10.3	73.1±16.9	69.9±16.8	$^{W}p=0.124$	$^{Base}p=0.975$ $^{Follow}p=0.137$ $^{End}p=0.866$
Control group (n=52)	70.9±8.7	65.4±22.1	69.5±17.6	$^{W}p=0.703$	
	Monocytes (%)				
Intervention group (n=52)	3.8±2.3	4.9±4.4	6.4±4.9	$^{W}p^{*}=0.003$	$^{Base}p=0.327$ $^{Follow}p=0.135$ $^{End}p=0.990$
Control group (n=52)	3.4±1.3	6.8±4.9	6.6±4.7	$^{W*}p=0.000$	
	Eosinophil (%)				
Intervention group (n=52)	2.3±2.1	2.8±3.7	3.5±4.5	$^{W}p=0.614$	$^{Base}p=0.536$ $^{Follow}p=0.378$ $^{End}p=0.291$
Control group (n=52)	2.8±4.2	3.7±5.1	2.6±2.7	$^{W}p=0.907$	
	Basophil (%)				
Intervention group (n=52)	0.02±0.1	0.10±0.3	0.10±0.3	$^{W}p=0.273$	$^{Base}p=0.562$ $^{Follow}p=0.081$ $^{End}p^{*}=0.031$
Control group (n=52)					

Significant P*<0.05. Non-parametric tests across 3-timelines: Friedman Rank test (Within sample differences i.e. WP) and Kruskal-Wallis H test (between samples differences i.e. intervention verses control).

White blood cell (WBC) count changes and their differential counts during three time periods (baseline, follow-up, and end line) for the intervention group and the control group are shown in table 2. At baseline, the total WBC count was 9.7 ± 10.5 X103/µL; at the end of the study, it was 7.7 ± 4.6 X103/µL. With a p-value of 0.021, which indicates a significant difference between the two groups, the control group's total WBC count similarly showed a slight reduction, going from 8.4 ± 2.5 X103/µL at baseline to 7.5 ± 7.2 X103/µL at the end line. The percentage of lymphocytes dropped marginally from 22.7 ± 8.8 at baseline to 20.1 ± 11.7 at the end of the study. Lymphocytes in the Control Group varied, but not significantly. The percentages of neutrophils stayed mostly constant with minor variations. The intervention group's monocyte percentage rose from 3.8 ± 2.3 at baseline to 6.4 ± 4.9 at the end (p = 0.003). The control group's monocyte count increased significantly from 3.4 ± 1.3 at baseline to 6.6 ± 4.7 at the end line, with a p-value of less than 0.0001, indicating that the control group's monocyte count also increased significantly. From 2.3 ± 2.1 at baseline to 3.5 ± 4.5 in the end, the intervention group's eosinophil percentage increased non-significantly. Likewise, the control group's eosinophil percentage varied but did not significantly alter (WP = 0.907). The intervention group's basophil percentage rose from 0.02 ± 0.1 at baseline to 0.10 ± 0.3 at the end line (p = 0.031), indicating a significant rise in basophils over time.

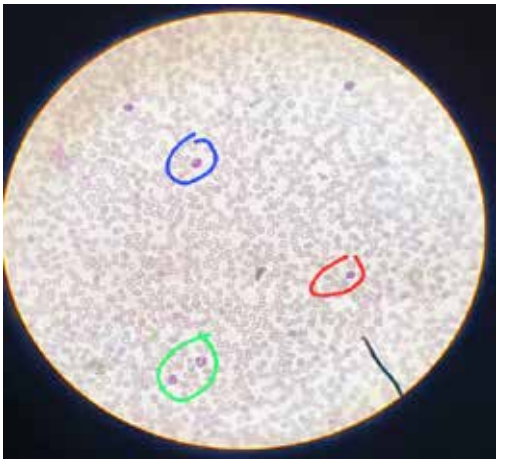

Figure 1(a): In 40x high power field showing hypochromic erythrocytes. White blood cells are mature and show normal distribution. Green circle-Neutrophils, blue circle - Monocyte, red circle -lymphocyte. PBF showing normocytic hypochromic anaemia (Before intervention)

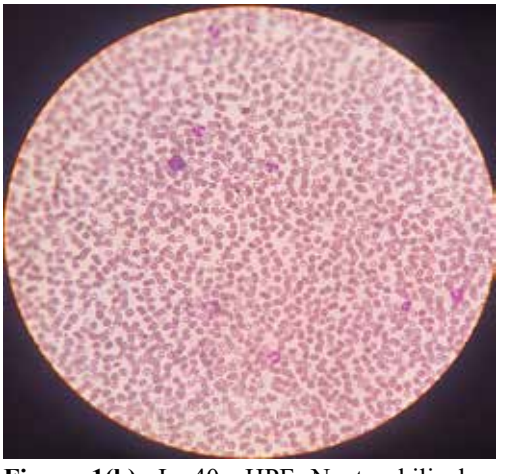

Figure 1(b): In 40x HPF, Neutrophilic leucocytosis with hypochromic anaemia. (Before intervention)

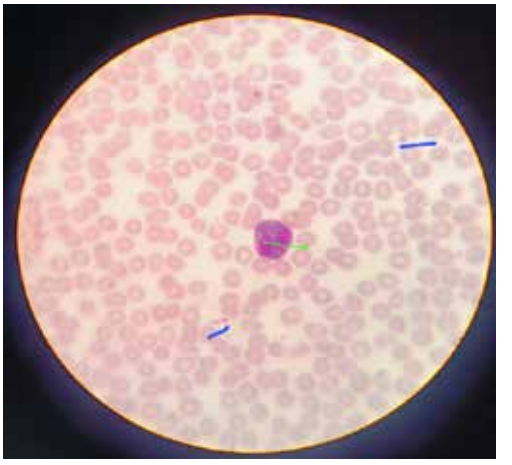

Figure 1(c): In 100X microscopic field, in PBF, it showed red blood cells are normochromic. (After intervention).

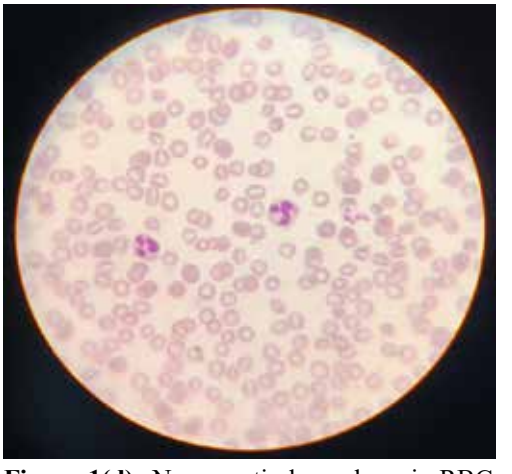

Figure 1(d): Normocytic hypochromic RBC and two neutrophils in PBF (After intervention).

Discussion

The results of this study on white blood cell (WBC) counts and their differential counts among patients with breast cancer receiving chemotherapy along with a nutritional intervention (egg protein, omega-3 fatty acids, and vitamin D) offer crucial information about how nutritional supplements affect immune modulation. There are a number of similarities and differences between these results and those from other domestic and foreign research. Both the intervention and control groups in this study had a small drop in the total WBC count, with a significant difference (P = 0.021) between the two groups. This outcome is in line with prior research that found that chemotherapy lowers WBC numbers, mostly as a result of myelo-suppression brought on by the drug. Crawford J, for instance, discovered that neutropenia is defined as a condition in which the absolute neutrophil count (ANC), or the number of neutrophils in the blood, falls below normal levels (i.e., less than 2000 cells per milliliter of blood), with the ANC measurement determining the severity of the condition1. Likewise, comparable patterns in WBC counts were identified, highlighting the similarities of immunological suppression brought on by chemotherapy.[10,11] Although the confounding effect of Filgrastim, which was given to both groups following chemotherapy, was probably a major factor mitigating the overall WBC reduction, the significant difference in WBC counts between the groups in this study may have been related to the influence of nutritional supplementation, which may have modulated immune responses to some extent. In this study, the intervention group's lymphocyte percentages decreased slightly (22.7 ± 8.8 to 20.1 ± 11.7), but not statistically significantly. Likewise, it was discovered that lymphocyte counts frequently fall after chemotherapy, indicating immunological suppression brought on by cytotoxic therapies.[12] Found no appreciable changes in the number of lymphocytes after taking omega-3 fatty acid supplements, indicating that the lack of a discernible impact of nutritional interventions on lymphocytes in this investigation is in line with similar findings.[13] Omega-3 fatty acid supplementation was found to significantly preserve cell numbers in chemotherapy patients, which is interesting since it suggests that nutritional therapies may help sustain adaptive immune responses.[14] This discrepancy could result from differences in the chemotherapy regimens employed in these studies, dosage, or study design. Prior to, during, and following therapy, the white blood cell (WBC) count was 6.56 ± 2.39, 5.53 ± 2.22, and 6.23 ± 3.48, according to a study. The platelet counts were 287.56 102.27, 376.40 135.34, and 306.91 127.25 prior to, during, and following treatment.[15] Additionally, it was discovered that the cases' mean WBC counts, neutrophil and lymphocyte percentages (6.96±7.22, 54.75±13.1%, and 38.19±12.70%, respectively) were greater than those of the controls (5.47±1.57, 44.39±8.78%, and 8.82±15.97%, respectively).[16] This study emphasizes how difficult it is to evaluate how nutrition affects WBC recovery in patients with breast cancer receiving Filgrastim treatment. Although nutritional therapies might influence the immune system, it can be challenging to distinguish their effects from those of pharmaceutical activation. Alternative immunological biomarkers and study designs that more clearly differentiate dietary contributions from filgrastim-induced hematopoiesis should be included in future investigations.

Recommendations

1. To more accurately evaluate the independent effects of nutritional therapies in chemotherapy patients using Filgrastim, future studies should include immunological biomarkers other than the total WBC count.
2. Given the notable rise in monocytes and basophils, it is recommended that distinct WBC subtypes be examined independently in order to comprehend how they contribute to immune regulation during chemotherapy.
3. To elucidate the direct effect of nutrition on hematologic recovery, longitudinal studies involving control groups that do not receive Filgrastim are required.

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