International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Determination of Hematological and Coagulation Parameters changes among breast cancer women under chemotherapy at National Cancer Institute (NCI)-Al-Gazira State-Sudan

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Abstract

Background: Breast cancer, which accounts for around 34% of all female cancers, is a major global health concern with a considerable prevalence in Sudan. By investigating the impact of sociodemographic characteristics and lifestyle decisions on the development of breast cancer in Sudanese women, this study seeks to close the knowledge gap. This study targeted breast cancer patients and changes during coarse of chemotherapy in some of hematological parameters, such as hemoglobin, white blood cell, platelet count and coagulation profile in order to focus on what phase changes occurred, the study conducted at the National Cancer Institute (NCI) in Gezira state.

Method: the study recruited 70 females with breast cancer, new cases, under chemotherapy with different number of doses. Healthy subjects well used as control group for comparisons, blood samples collected used for complete blood count assessment and prothrombin time (PT) and activated partial thromboplastin time (APTT) as n INR. Data collected analyzed via statistical package of social science (SPSS) version 20.

Result: Considering the affection of chemotherapy dose used by patients, measured parameters, it revealed that there were significant differences in mean+SD of parameters PT, APTT, INR, and Hb as p value for each <0.05 and the rest showed no significant p value >0.05. Comparison of measured parameters mean+SD before and after chemotherapy doses showed that there was no significant difference between pre chemotherapy patients and post chemotherapy patients in Hb, TWBCs, Platelet, PT, APTT and INR.

Key words: Breast cancer, chemotherapy

Introduction

The presentation, histologic type, molecular biomarkers, prognosis, and treatment outcomes of breast cancer vary greatly, making it a complicated illness with a wide range of clinical and pathological features. Overall survival and fatality rates are significantly impacted by the stage of the disease at diagnosis. Just 16% of women receive a stage I diagnosis, whereas 54% receive a stage II diagnosis. [1].

The most frequent cancer in women and the primary cause of cancer-related mortality worldwide is breast cancer. It is the most prevalent cancer among women in sub-Saharan Africa. Risk factors for breast cancer include age, location, menstrual history, family history, null parity, and the presence of benign breast illness. When a patient is diagnosed with cancer, they may have comorbidities, particularly if they are elderly. 20 to 35% of women with breast cancer have one or more comorbidities at the time of diagnosis, according to earlier research. The management of breast cancer is further complicated by the existence of comorbidities at the time of diagnosis. Risk factors for breast cancer include cardiovascular illness, urbanization, and communicable diseases. Examining comorbidities in conjunction with breast cancer is crucial not only because they may be risk factors for the disease but also because they may have an impact on the disease's prognosis, treatment options, and stage at diagnosis [2].

Breast cancer was more common in countries with higher socioeconomic level, especially in Europe. The death rates from breast cancer are higher in low-sociodemographic countries than in high-income countries, despite the fact that the disease is less common there. The African Region is not far behind the Eastern Mediterranean Region, which has the highest age-standardized death rate. In 2019, high-income nations had the highest age-standardized rate of Years Lived with Disability (YLD) per 100,000 people, while low-income countries had higher age-standardized rates of Disability-Adjusted Life Years and Years of Life Lost per 100,000 people [3].

Chemotherapy: Neoadjuvant chemotherapy (NAC), adjuvant chemotherapy (AC), and salvage chemotherapy are the three types of chemotherapy used to treat breast cancer. In cases of early breast cancer, chemotherapy could lower the chance of recurrence by about 30%. NAC could eradicate micrometastatic lesions, transform incurable breast cancer into resectable breast cancer, and downstage the breast and axilla for getting breast conservation in cases of operable breast cancer. Patients with big tumors, many axillary lymph nodes (ALNs) involved, and aggressive subtypes—particularly triple-negative and HER2-positive breast cancer—should get NAC. Applying NAC to aggressive breast cancer subtypes may assess therapy response, forecast cancer prognosis, and direct future treatment choices [4].

Chemotherapy has varying effects on blood cell counts and metabolic profiles. It acts as an alkalizing agent and eventually eliminates the hematopoietic stem cells in the bone marrow [5]. Chemotherapy typically causes cells to die or stop proliferating by preventing the synthesis of proteins, microtubules, and deoxyribonucleic acid (DNA) [6]. By covalently attaching to the deoxyribonucleic acid of bone marrow cells and creating intra- and inter-strand cross-links, chemotherapeutic medicines damage deoxyribonucleic acid during replication [7]. Hemoglobin, leukocytes, and platelets all decrease. Hemoglobin and chemotherapy did not significantly correlate, according to a study on the subject[8].

Previous studies on breast cancer have also shown a hypercoagulable state with increased tissue factor, fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (APTT). Treatments for breast cancer, including hormone therapy, chemotherapy, and surgery, aggravate and contribute to this hypercoagulable state [9]

Material and Method

This study conducted as case control one in National Cancer Institute (NCI) in Gezira state, targeted breast cancer patients, they were 70 patients, divided to newly diagnosed 10 (14.3%), 50 (71.4%) received chemotherapy and last 10 (14.3%) with less than 10 doses of. Chemotherapy. Whole blood samples collected for complete blood count collected in EDTA added blood containers, assessment by automated hematology analyzer XP300-Sysmex. Coagulation profile included prothrombin time (PT), activated partial thromboplastin time (APTT) and INR via Coatron device (Biosystem). Healthy subjects were included as control group; same parameters were assessed for them to compare with. Data analyzed by means of statistical package of social science (SPSS) version 20, ANOVA tests for comparison and Pearson correlation as well.

4. Result

This study was conducted between June 2021 to Sep 2021.The study involved 70 female breast cancer patients and 50 apparently healthy individual were enrolled in this study, the mean age of female breast cancer was 58.2 years , their disease duration was between 2 to 36 (Months) with means 11.4± 6.7,also the maximum chemotherapy dose was 18 with means 5.9±4.5 All patients and control group were tested for HB, WBC, PLTS, PT, PTT and INR with means of case group(11.2±1.7, 7.12±4.0, 372.3±193.4, 12.5±1.9 second, 33.3±8.4 second and 0.9± 0.2)respectively .Furthermore ,the means of HB, WBC, PLTS, PT, PTT and INR with means among control group was (11.8±0.9, 5.6±1.1, 268.9±66.9, 13.7±0.9 second ,33.3±3.8 second and 0.9± 0.1).

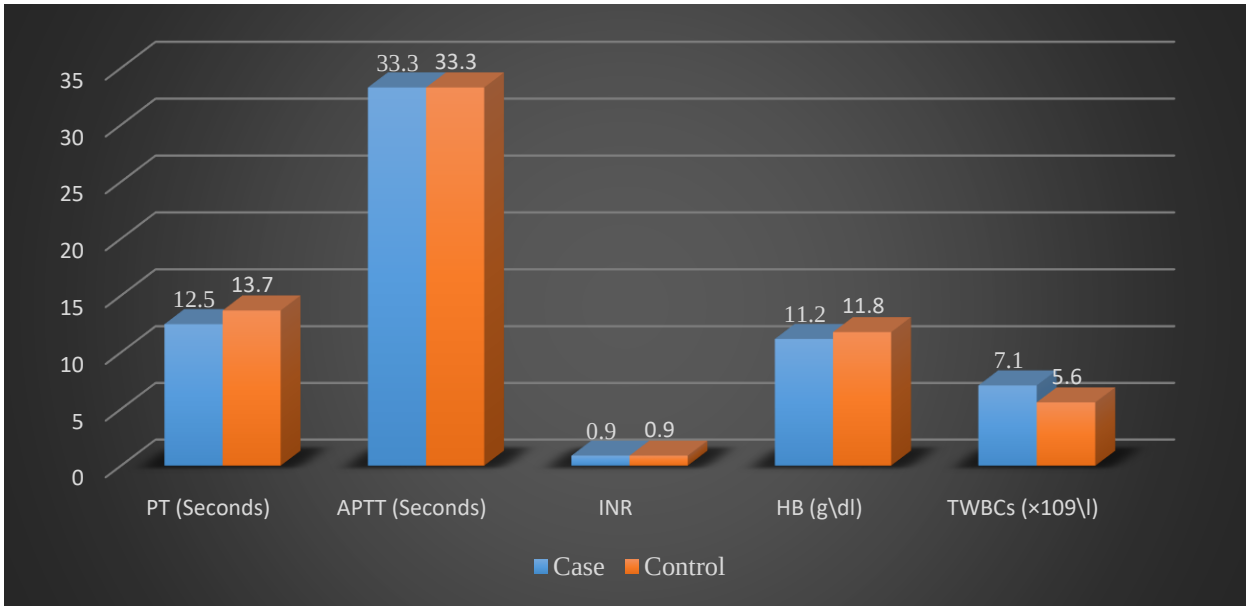

Figure 1: Mean of study variables in case and control

Table 1: Patients with breast cancer undergoing chemotherapy compared with their control for the parameters. PT: There was significant decrease in PT among cases when compared with control (12.5 ± 1.9 and 13.7 ± 0.9) second respectively (*P. Value* 0.000*). PTT: There was no significant difference in APTT (*P. Value*= 0.989) mean of APTT among case = (33.3 ± 8.4 second) while among control = (33.3 ± 3.8 second). INR: There was no significant difference in International Normalized Ratio, the mean of INR among case = 0.9 ± 0.2 while among control = 0.9 ± 0.1 (*p. Value*=0.745). Hb: There was significant

decrease in HB mean of case = (11.2 ± 1.7) (g\dl) in comparison of control = (11.8 ± 1.1) p. value less than 0.05 (*P. Value* 0.018*). White blood cell count (WBCS): There was significant increased (*P. Value* 0.004*) the mean of WBCS among case = 7.1 ± 4.0 ($\times 10^9$\l) while among control= 5.6 ± 1.1($\times 10^9$\l). platelet (PLTS): There was significant increased (*P. Value* 0.000*) mean of among case =372.3 ± 193.4 ($\times 10^9$\l) while among control=268.9 ± 66.9 ($\times 10^9$\l).

Table 1: Comparisons of study variables between case and control

Variables	Case (n=70)	Control (n=50)	P. value
PT (Seconds)	12.5 ± 1.9	13.7 ± 0.9	0.000*
APTT (Seconds)	33.3 ± 8.4	33.3 ± 3.8	0.989
INR	0.9 ± 0.2	0.9 ± 0.1	0.745
Hb (g\dl)	11.2 ± 1.7	11.8 ± 1.1	0.018*
TWBCs ($\times 10^9$\l)	7.1 ± 4.0	5.6 ± 1.1	0.004*
Platelets ($\times 10^9$\l)	372.3 ± 193.4	268.9 ± 66.9	0.000*

P. value less than 0.05 was considered significant

According to normal value there were 47(67.1%) with Anemia and 23(32.9%) with normal hemoglobin (Hb), 16(22.9%) with Leukopenia, 13(18.6%) Leukocytosis and 41(58.6%) were have Normal TWBCs .6(8.6%) were Thrombocytopenia, 28(40) Thrombocytosis and 36(51.4%) have Normal platelets count as in table 2.

Table 2: Frequency and Percent of Hb, TWBCS and PLTS

		Frequency	Percent
HB (g\dl)	Anemia	47	67.1
	Normal Hb	23	32.9
	Total	70	100.0
TWBCs ($\times 10^9$\l)	Leukopenia	16	22.9
	Normal TWBCs	41	58.6
	Leukocytosis	13	18.6
	Total	70	100.0
Platelets ($\times 10^9$\l)	Thrombocytopenia	6	8.6
	Normal platelets count	36	51.4
	Thrombocytosis	28	40.0
	Total	70	100.0

Comparison of measured parameters mean+SD before and after chemotherapy doses showed that there was no significant difference between pre chemotherapy patients and post chemotherapy patients in Hb, TWBCs, Platelet, PT, APTT and INR as in table 3.

Table 3: Comparisons of study variables pre- chemotherapy and post- chemotherapy

Variables	Pre- chemotherapy (n=10)	Post- chemotherapy (n=60)	P. value
PT (Seconds)	12.8 ± 1.2	12.5 ± 2.1	0.677
APTT (Seconds)	34.3 ± 3.6	33.1 ± 8.9	0.702
INR	1.0 ± 0.1	0.9 ± 0.2	0.977
HB (g\dl)	10.7 ± 1.9	11.3 ± 1.7	0.351
TWBCs ($\times 10^9$\l)	7.9 ± 2.5	7.0 ± 4.3	0.519
Platelets ($\times 10^9$\l)	424.6 ± 143.8	363.6 ± 200.1	0.359

Considering the affection of chemotherapy dose used by patients, measured parameters, it revealed that there were significant differences in mean±SD of parameters PT, APTT, INR, and Hb as p value for each <0.05 and the rest showed no significant p value >0.05 as in table 4. (*ANOVA test was used to calculate p. value)*

Table 4: Multiple Comparisons of measured parameters according to dose of chemotherapy

Variables	Dose of chemotherapy (I)	Dose chemotherapy (II)	Mean(I)	Mean (II)	P. value
PT (Seconds)	Without chemotherapy(n=10)	Less than 10 dose (n=50)	12.8 ±1.2	11.8 ± 0.8	0.066
		More than 10 dose(n=10)		15.8 ± 3.3	0.000*
	Less than 10 dose (n=10)	More than 10 dose(n=10)	11.8 ±0.8	15.8 ± 3.3	0.000*
APTT (Seconds)	Without chemotherapy(n=10)	Less than 10 dose(n=50)	34.3 ±3.6	31.9 ± 5.8	0.409
		More than 10 dose(n=10)		39.3 ± 17.1	0.171
	Less than 10 dose(n=50)	More than 10 dose (n=10)	31.9 ±5.8	39.3 ± 17.1	0.011*
INR	Without chemotherapy(n=10)	Less than 10 dose(n=50)	1.0 ± 0.1	0.9 ± 0.1	0.242
		More than 10 dose(n=10)		1.3 ± 0.3	0.000*

	Less than 10 dose(n=50)	More than 10 dose(n=10)	0.9 ± 0.1	1.3 ± 0.3	0.000*
HB (g\dl)	Without chemotherapy(n=10)	Less than 10 dose (n=50)	10.7 ±1.9	11.6 ± 1.3	0.099
		More than 10 dose (n=10)		9.5 ± 2.2	0.086
	Less than 10 dose (n=50)	More than 10 dose (n=10)	11.6 ±1.3	9.5 ± 2.2	0.000*
TWBCs ($\times10^9$\l)	Without chemotherapy(n=10)	Less than 10 dose (n=50)	7.9 ± 2.5	6.6 ± 3.5	0.329
		More than 10 dose (n=10)		9.3 ± 6.7	0.441
	Less than 10 dose (n=50)	More than 10 dose (n=10)	6.6 ± 3.5	9.3 ± 6.7	0.051
Platelets ($\times10^9$\l)	Without chemotherapy(n=10)	Less than 10 dose (n=50)	424.6 ± 143.8	374.3 ± 186.9	0.456
		More than 10 dose (n=10)		309.8 ± 261.5	0.190
	Less than 10 dose (n=50)	More than 10 dose (n=10)	374.3 ± 186.9	309.8 ± 261.5	0.340

Regarding to the duration of the disease, patients sorted to (less than 12 months and more than 12 months). Comparing measured parameters between both groups of durations showed that there was significant difference of PT and INR (p=0.017 and 0.026), by the other hand Hb has significant decreased with duration of disease (p=0.025) while other parameters TWBCs, Platelets and APTT hasn't significant differences with disease duration as in table 5.

Table 5: Comparisons of study variables according to duration of disease

Variables	**≤ 12 months (n=51)**	**> 12 months (n=19)**	**P. value**
PT (Seconds)	12.0 ± 0.9	13.9 ± 3.2	0.017*
APTT (Seconds)	32.5 ± 5.3	35.4 ± 13.6	0.377
INR	0.9 ± 0.1	1.1 ± 0.3	0.026*
HB (g\dl)	11.5 ± 1.5	10.4 ± 2.1	0.025*

TWBCs ($\times 10^9$\l)	7.3 ± 3.3	6.8 ± 5.7	0.668
Platelets ($\times 10^9$\l)	400.2±158.1	297.4 ± 256.6	0.116

T test was used to calculate p. value

Considering age, patients were sorted to 2 groups, ≤ 50 years (n=22) and > 50 years (n=48), comparison of measured parameters between the 2 groups, showed that there were no significant differences as p value for each was >0.05 as in table 6.

Table 6: Comparisons of study variables according to age of patients

Variables	**≤ 50 years (n=22)**	**> 50 years (n=48)**	**P. value**
PT (Seconds)	12.5 ± 1.4	12.6 ± 2.2	0.851
APTT (Seconds)	32.7 ± 6.1	33.6 ± 9.3	0.663
INR	0.9 ± 0.1	1.0 ± 0.2	0.481
HB (g\dl)	11.3 ± 2.2	11.1 ± 1.5	0.721
TWBCs ($\times 10^9$\l)	8.1 ± 5.6	6.7 ± 3.1	0.191
Platelets ($\times 10^9$\l)	384.5 ± 220.1	366.7 ± 182.2	0.724

Pearson's correlation of measured parameters and with dose of chemotherapy revealed positive correlations with PT, APTT and INR with significant difference for each of PT and INR (p value<0.05) and negative correlations with Hb, TWBC and platelet with significant difference only for Hb (p value <0.05). duration of the disease and measured parameters has positive correlation for each of PT, APTT and INR with significant differences for PT and INR and negative correlations with Hb, TWBC and platelet with no significant difference as p value for each >0.05 as in table 7 and figures 2—7.

Table 7: Correlations between dose of chemotherapy and duration of disease to study variable

		PT	**APTT**	**INR**	**HB**	**TWBCs**	**Platelets**
Dose of chemotherapy	Pearson Correlation	.482*	.142	.461*	-.273*	-.015	-.221
	P. value	.000	.241	.000	.022	.899	.066
	N	70	70	70	70	70	70
Duration of disease	Pearson Correlation	.530*	.161	.519*	-.299*	-.024	-.238*
	P. value	.000	.183	.000	.012	.843	.048
	N	70	70	70	70	70	70

Pearson Correlation *was used to calculate p. value*

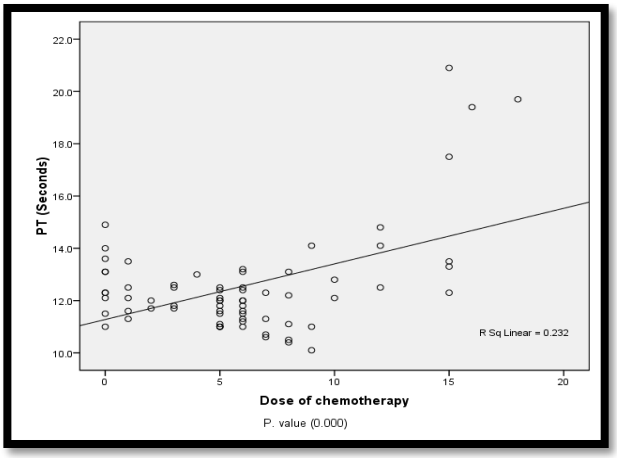

Figure 2: Correlations between dose of chemotherapy and PT

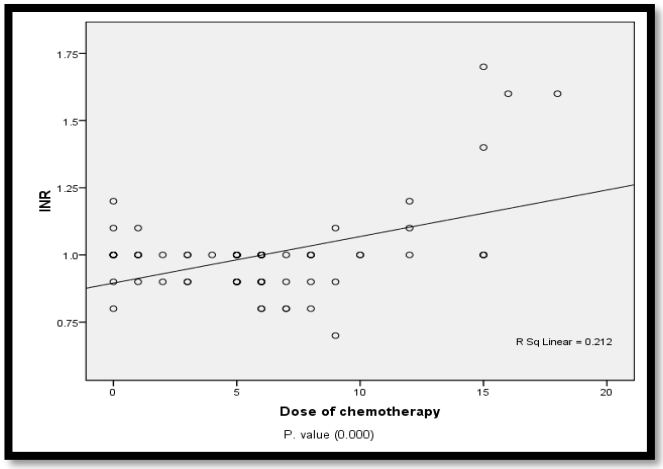

Figure 3: Correlations between dose of chemotherapy and INR

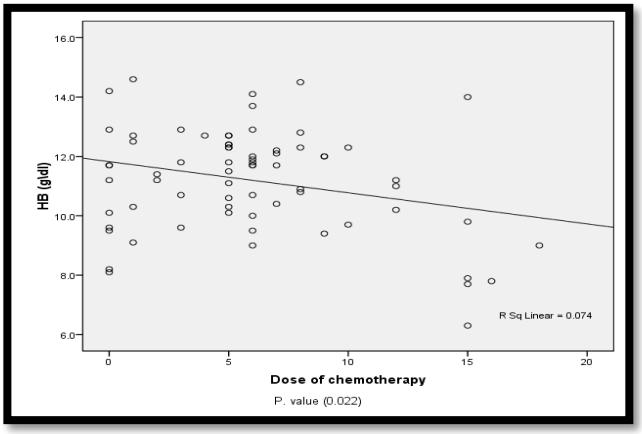

Figure 3: Correlations between dose of chemotherapy and Hb

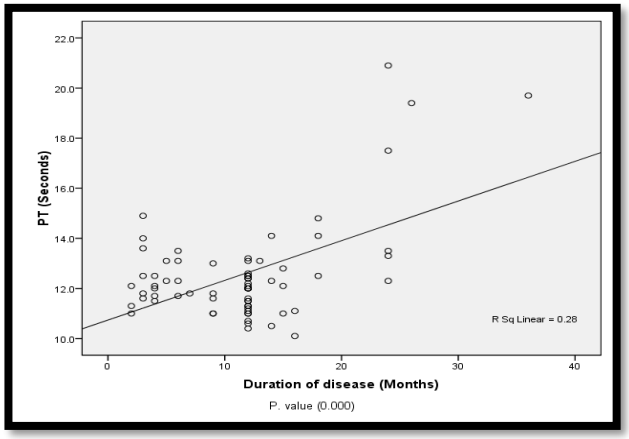

Figure 5: Correlations between duration of disease and PT

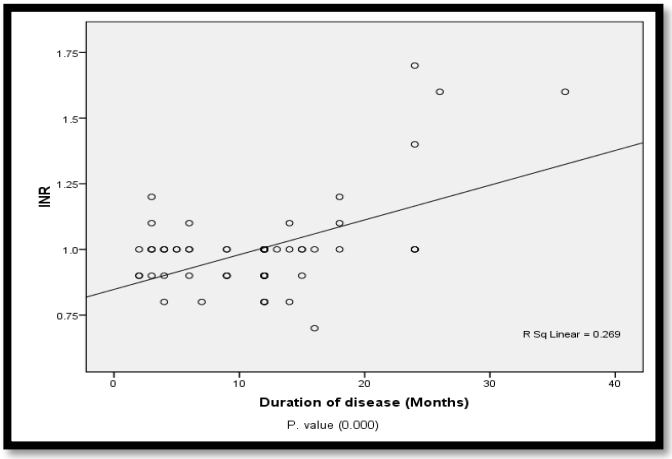

Figure6: Correlations between duration of disease and INR

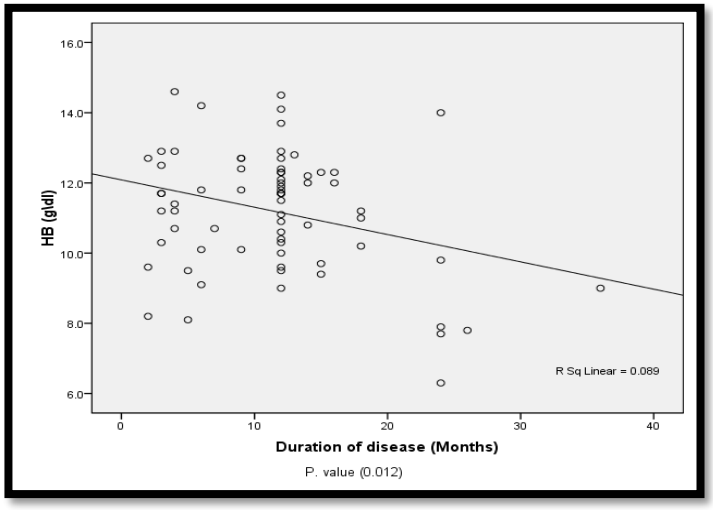

Figure 7: Correlations between duration of disease and HB

Discussion

Worldwide, breast cancer is the most prevalent type of cancer and the primary cause of cancer-related death among women. Postoperative systemic therapies, such as chemotherapy, endocrine therapies, immunotherapy using monoclonal antibodies targeted at tumor receptors, and radiation, are used to treat nonmetastatic breast cancer. The mainstay of treatment for breast cancer is chemotherapy. In light of chemotherapy, extensive treatment can be administered to lower the risk of distant metastases and recurrence. By assessing the advantages of comprehensive treatment, patients' prognoses can be somewhat predicted [10].

This a cross-sectional study conducted to compare hematological and coagulation parameters in 70 female breast cancer patients on chemotherapy and 50 healthy controls. The patients' mean age was 58.2 years, with a mean disease duration of 11.4 months and a mean chemotherapy dose of 5.9. Compared with controls, patients showed significantly lower hemoglobin and PT, and significantly higher WBC and platelet counts, while APTT and INR showed no significant differences. Anemia was present in 67.1% of patients, leukocyte and platelet abnormalities were common. No significant differences were found between pre- and post-chemotherapy values overall. However, chemotherapy dose and disease duration were significantly associated with changes in PT, INR, and Hb. Age showed no significant effect on any parameter. Correlation analysis demonstrated positive correlations of chemotherapy dose and disease duration with PT and INR, and negative correlations with hemoglobin, indicating chemotherapy and longer disease duration mainly affect coagulation and anemia status.

A partial agreement obtained with an Indian study conducted involving 44 female patients aged 18 years and older. Patients diagnosed with breast cancer will be included in the study Demographic e collected and pre- and postchemotherapy investigations—including Complete Blood Count (CBC), Coagulation Profile were assessed over six cycles, with intervals determined by the patient's disease progression. Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), International Normalized Ratio (INR) across different chemotherapy cycles. The significance level for all tests will be set at p-value <0.05 [11].

Another partial agreement with a study targeted hematological profiles were collected from 267 breast cancer patients who attended the cancer treatment center from September 2017 to August 2021. The study compared the mean difference between the hematological profiles at zero and after the 4th and 8th cycles of treatment. Of the total participants, 91% were females, and the median age of the study participants was 45 years. white blood cell, and hemoglobin values, were significantly reduced after the initiation of cancer treatment, while the platelet count and red cell distribution width were significantly increased. The prevalence of anemia was 21.7% 22.7%, and 26.4% before, during, and after the initiation of cancer treatment, respectively. The prevalence of leukopenia before, during, and after treatment was 9.7%, 18.8%, and 15.1%, respectively[12].

An agreement with a study assessed the effects of chemotherapy on clinical, hematological and biochemical profile of breast cancer patients undergoing chemotherapy in the Cape Coast Teaching Hospital, randomly sampled 51 patients diagnosed with breast cancer and scheduled to start chemotherapy.

Blood was collected for hematological profiles (hemoglobin (Hb), white blood cell (WBC) count, platelets (PLT) for day 1, day 21 and day 42 of their chemotherapy cycles. Majority of the participants were within 46-60 years. Throughout chemotherapy cycles. Hemoglobin though insignificant, decreased after the second cycle but increased sharply after the third cycle (P=0.281). White blood cells (WBC) significantly decreased throughout cycles (P=0.008) whereas high density lipoprotein (P=0.014) increased throughout cycles. Throughout cycles, chemotherapy had significant adverse effect on the white blood cells (WBC) in patients undergoing treatment [13].

The present study was showed positive correlation between dose and duration of the disease to hematological and coagulation parameters changes this finding agreed with study done by Preeti Chauhan et al (2016) [14].

Conclusion

There was a significant alteration in hematological parameters and coagulation parameters (PT test) and this alteration of hematological and coagulation parameters increased according to number of dose and duration of disease in breast cancer women.

Recommendation

1. Investigation of HB, WBCS, PLT count, PT, INR and PTT must be done routinely for patients with breast cancer under treatment to help for good prognosis of patients
2. Other investigation of hematological parameters must be done (D. dimer, fibrinogen)
3. Other study with large sample size must be applied with comparison hormonal therapy and chemotherapy treatment on breast cancer patients.
4. Breast cancer patient's treatment Protocol should be included drugs to improve the immunity, prevent bleeding tendency and supplementary drugs for increase HB between cycles of chemotherapy; Chemotherapy induced anemia can be treated with erythropoiesis stimulated agents, RBC transfusions.

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