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EFFECT OF DOXORUBICIN AND CYCLOPHOSPHAMIDE ON SOME HEMATOLOGICAL PARAMETERS IN WOMEN WITH BREAST CANCER IN IRAQ

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Abstract

The study of was conducted to evaluate some hematological parameters among breast cancer women and apparently healthy individuals in Iraqi women at medical city hospital 75 breast cancer patients and 15 control healthy women, individual were studied between November (2019) and February (2020). The aims of this study are to evaluate the effect of chemotherapy especially doxorubicin and cyclophosphamide on blood parameters such as complete blood count and RBCS indices. patients were divided in to five groups and each group contain 15 patient women with breast cancer. The hematological test which includes red cell count, platelets count, hemoglobin, packed cell volume, Platelet Distribution Width (PDW), Mean platelet volume (MPV) and Plateletcrit (PCT), MCV, MCH, MCHC. Total and differential leukocytes count. The results of RBCS in treated groups show significant difference ($p<0.05$); hemoglobin decreased significantly ($p<0.01$); PCV% reduced significantly ($p<0.01$); platelets show significantly variation ($p<0.05$); PDW increased significantly while PDW decreased significantly ($p<0.01$); MPV and PCT increased significantly ($p<0.05$). MCV shows non-significant variation. MCH and MCHC shows significant decrease ($p<0.05$). Total leukocytes were non-significant neutrophils ($2\text{-}7\times10^3/\mu l$) reduce significantly ($P<0.05$) among treated groups. Lymphocytes show significant reduction ($P<0.05$). Monocytes increased significantly ($P<0.01$). Eosinophils show non-significant difference while Basophils reduce significantly ($P<0.05$). Differential leukocytes for neutrophils, lymphocytes, monocytes and basophils show a significant increase while eosinophils were non-significant.

Key words: health, environmental; Hematological parameters

Introduction

Cancer is a term used for diseases where abnormal cells divide uncontrolled and may invade other tissues (Lodish *et al*., 2000). Breast carcinoma is one of the most popular neoplasms in women and is a major cause of deaths in the world (Polyak, 2001). In Iraq, it is the first cancer in ranking diagnosed in women (Arkan, 2016). The rate of breast cancer increased between the age of 60 to 69 year (Al-Hashimi, 2014). Surgery and Chemotherapy are used for treatment patients, the type of chemotherapy that are used for treatment patient are doxorubicin and cyclophosphamide. Chemotherapy for breast cancer destroy constantly dividing breast cancer cells. Chemotherapy affects normal, healthy cells as well as breast cancer cells; it may cause hair loss, anemia and diarrhea as side effect. A complete blood count (CBC) parameter is a blood test that provides valuable information on the types and numbers of blood cells, especially red blood cells, white blood cells and platelets. CBC allows health professionals to test any signs, such as fatigue, tiredness or swelling, It also helps in the diagnosis of other diseases (Ali, 2014). RBCs of patients affected by breast cancer are more sensitive to the denaturing action (Croci *et al*., 2002). Most of the patients with breast cancer who diagnosed with different stages will need chemotherapy. These chemotherapeutic agents had high antiemetic potential and need antiemetic drugs prior to it. other common side effects are hair loss, fatigue, abdominal pain, cardiotoxicity and possible renal toxicity. During adjuvant chemotherapy, low blood counts are observed as a side effect of chemotherapies. (Miller and Heilmann, 1988). White blood cell count (WBC), an inflammatory biomarker, has ability of both predictor of certain diseases and a marker of infection. Even within the normal range of WBC count, it has been correlated

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with the frequency and death of cancer and coronary atherosclerotic diseases. (Margolis *et al*., 2007).

Materials and Methods

In this study 75 women breast cancer patients enrolled with invasive breast cancer before surgery and who underwent to surgery and four treatment session of chemotherapy with 15 healthy women as control. The patients were divided into five group according to chemotherapy session into: Before treatment, treatment one, treatment two, treatment three, treatment four to investigate the effect of chemotherapy on each session on complete blood picture in medical city hospital. List of questionnaires was used to take information related to Age, highest, Wight, social status, contraceptive, day of cycle, the stage of the disease, history of disease and other treatment for both patients and control. Most of the patients with breast cancer who diagnosed with different stages will need chemotherapy. Chemotherapy protocols are the most usable one which was given to patients in our study is the protocol that contains 2 drugs, doxorubicin and cyclophosphamide. These chemotherapeutic agents had high antiemetic potential and need antiemetic drugs prior to it. Other common side effects are hair loss, fatigue, abdominal pain, cardiotoxicity and possible renal toxicity. Doxorubicin given in a dose of 60 mg/m^2 and diluted in 100 cc normal saline and given in dripping within 10-15 mins., while cyclophosphamide given in a dose of 600 mg/m^2 and diluted in 500 cc normal saline) and given within 60 mins. The patients under treatment by chemotherapy their duration are 8 months mainly (one session each 21 day).

Hematological Parameters

Two milliliters of venous blood was collected from each woman patient (before chemotherapy treatment) and control to test the hematological parameters the 2.0 ml dispensed into Ethylene diamine tetra acetic acid (EDTA tube) which contains an anticoagulant that was used for the hematological test, red cell count, platelets count. Total and differential white blood cells count by using complete blood picture.

Complete Blood Picture Device: Fully automated hematology analyzer, Device that was used for perform complete blood picture, Designed to measure up to 20 parameters using whole blood from an open inlet.

Results

Results of red blood cell obtained from seventy five with breast cancer patients and fifteen healthy individuals are shown in table 1.

The RBCs in different groups showing different variation ($P \leq 0.05$) in breast cancer groups (4.38 ±0.11; 4.29 ±0.17; 4.57 ±0.10; 4.24 ±0.14; 4.07 ±0.13) respectively in comparison with control group (4.29 ±0.12). That fourth treated group (4.29 ±0.12) shows significant decrease when compared with 2nd treated group (4.57 ±0.10). Hemoglobin values decreased significantly ($P \leq 0.01$) in breast cancer groups (11.36 ±0.34; 11.42 ±0.65; 11.54 ±0.45; 11.82 ±0.35; 11.19 ±0.34) respectively in comparison with the control groups (13.83 ±0.33). (35.02 ±1.02; 35.02 ±1.02; 35.40 ±1.41; 36.20 ±0.97; 36.20 ±0.97; 32.99 ±1.10) when compared with control group (39.34 ±0.62). Before; 1st, 2nd, 3rd treated groups show more prominent decrease in comparison

Table 1: Comparison Between Different Groups in Blood Parameters.

Parameters	Mean + SE						LSD Value
	Control	Before	Treatment 1	Treatment 2	Treatment 3	Treatment 4	
RBCS (3.8-5.50×10^6/µl)	4.29 ± 0.12 ab	4.38 ± 0.11 ab	4.29 ± 0.17 ab	4.57 ± 0.10 a	4.24 ± 0.14 ab	4.29 ± 0.12 b	0.375 *
Hb (12-17gm/dl)	13.83 ±0.33 a	11.36 ± 0.34 b	11.42 ± 0.65 b	11.54 ± 0.45 b	11.82 ± 0.35 b	11.19 ± 0.34 b	1.207 **
PCV (36-50%)	39.34 ± 0.62 a	35.02 ± 1.02 b	35.38 ± 1.64 b	35.40 ± 1.41 b	36.20 ± 0.97 ab	32.99 ± 1.10 b	3.309 **
Platelets (150-400×10^3/µl)	332.40 ± 15.48 ab	314.93 ± 11.12 b	315.93 ± 18.75 b	353.86 ± 23.17 ab	395.67 ± 36.86 a	354.13 ± 35.03 ab	71.13 *
PDW (15-17%)	16.62 ± 0.19 c	17.92 ± 0.32 ab	18.06 ± 0.31 a	17.45 ± 0.17 ab	17.31 ± 0.15 b	17.73 ± 0.22 ab	0.671 **
MPV (7-11ft)	8.13 ± 0.20 ab	8.27 ± 0.17 a	8.01 ± 0.24 ab	7.99 ± 0.16 abc	7.50 ± 0.10 c	7.69 ± 0.11 bc	0.491 *
PCT (0.16-0.33%)	0.230 ± 0.01 b	0.249 ± 0.01 ab	0.242 ± 0.01 ab	0.271 ± 0.02 ab	0.295 ± 0.03 a	0.265 ± 0.02 ab	0.062 *
Means having with the different letters in same row differed significantly. *($P \leq 0.05$), **($P \leq 0.01$).							

Table 2: Comparison Between Different Groups in MCV, MCH and MCHC.

Parameters	Mean + SE						LSD Value
	Control	Before	Treatment 1	Treatment 2	Treatment 3	Treatment 4	
MCV (80-100ft)	85.21±1.19 a	80.00±2.22 a	79.80±2.91 a	80.88±2.73 a	84.61±1.75 a	85.85±2.29 a	6.358 NS
MCH (28-30pg)	29.70±0.44 a	26.21±0.96 b	26.41±1.15 b	26.95±1.08 b	27.24±0.75 ab	28.65±0.82 ab	2.541 *
MCHC (31-35gm/dl)	33.20±0.34 ab	32.67±0.27 ab	32.66±0.38 ab	32.44±0.32 b	33.39±0.24 a	33.16±0.18 ab	0.846 *
Means having with the different letters in same row differed significantly. *(P≤0.05), NS: Non-Significant.							

with control group. Platelets count decrease significantly (P≤0.05) in before and1st treated groups (314.93 ±11.12); (315.93 ±18.75) in comparison with 2nd (353.86 ±23.17); 3rd (395.67 ±36.86); 4th(354.13 ±35.03) and control group (332.40±15.48) respectively. PDW increased significantly (P≤0.01) in cancer groups (17.92 ±0.32; 18.06 ±0.31; 17.45 ±0.1;17.31 ±0.15; 17.73 ±0.22) in comparison with control groups (16.62 ± 0.19). MPV values show significant difference (P≤0.05) in cancer groups (8.27 ±0.17; 8.01 ±0.24; 7.99 ±0.16; 7.50 ±0.10; 7.69 ±0.11) in comparison with control group (8.13 ±0.20). The 3rd treated group increased (0.295 ±0.03) significantly (P≤0.05) in comparison with before treated; 1st, 2nd; 4th (0.249 ±0.01; 0.271 ±0.02; 0.265 ±0.02) and control groups (0.230 ±0.01) respectively.

Mean corpuscular volume values in breast cancer groups show non-significant differences (80.00 ±2.22; 79.80 ±2.91; 80.88 ±2.73; 84.61 ±1.75; 85.85 ±2.29) respectively in comparison with control group (85.21 ±1.19). Mean corpuscular hemoglobin decreased significantly (P≤0.05) in before; 1st, 2nd groups (26.21 ±0.96, 26.41 ±1.15, 26.95 ±1.08) in comparison with control group (29.70 ±0.44) while 3rd and 4th (27.24 ±0.75 and 28.65 ±0.82) show non-significant difference. Mean corpuscular hemoglobin concentration increased significantly (p<0.05) in 3rd treated group (33.39 ±0.24) in comparison with 2nd treated group (26.95 ±1.08) while before, 1st and 4th treated groups show non-significant difference (32.67 ±0.27; 32.66 ±0.38; 33.16 ±0.18) when compared with control groups (33.20 ±0.34). Total leukocytes count in all groups shows non-significant difference (7.73 ±0.52; 8.05 ±0.97; 7.89 ±0.73; 6.39 ±0.56; 7.08 ±0.58) in comparison with control (7.28 ±0.26). Absolute count of neutrophils shows significant increase (P≤0.05) in before group in comparison with four treated (1st,2nd.3rd.4th) groups (5.05 ±0.70; 4.12 ±0.45; 3.46 ±0.37; 4.22 ±0.55) and control group (4.43 ±0.37) while 3rd group shows less value (3.46 ±0.37).Absolute lymphocytes increased significantly (P≤0.05) in 1st groups (3.38 ±1.03) in comparison with before; 2nd, 3rd, 4th and control group (1.76 ±0.18; 2.58 ±0.20; 1.82 ±0.14; 1.50 ±0.19; 2.75 ±0.1). While before; 3rd and 4th shows non-significant differences. Absolute monocytes increased significantly (P≤0.01) in 2nd (0.966 ±0.11) in comparison with before; 3rd control group (0.44 ±0.07; 0.613 ±0.05; 0.413 ±0.05), While 1st(0.786 ±0.13), 3rd (0.613 ±0.05) and 4th (0.720 ±0.11) were non-significant. Absolute count of eosinophil were non-significant in all breast cancer groups (0.120 ±0.02; 0.160 ±0.04; 0.186 ±0.04; 0.106 ±0.02; 0.10 ±0.04) in comparison with control groups (0.180 ±0.02). Absolute basophils count decreased significantly (P≤0.05) in all cancer groups (0.08 ±0.01; 0.073 ±0.01; 0.073 ±0.01; 0.053 ±0.01; 0.086 ±0.01) in comparison with control group (0.146 ±0.03).

Table 3: Comparison Between Different Groups in Total WBC and Absolute Differential count.

Parameters	Mean + SE						LSD Value
	Control	Before	Treatment 1	Treatment 2	Treatment 3	Treatment 4	
WBC (4-10×10³/µl)	7.28 ± 0.26 a	7.73 ± 0.52 a	8.05 ± 0.97 a	7.89 ± 0.73 a	6.39 ± 0.56 a	7.08 ± 0.58 a	1.80 NS
Neutrophils (2-7×10³/µl)	4.43 ± 0.37 abc	5.64 ± 0.54 a	5.05 ± 0.70 ab	4.12 ± 0.45 bc	3.46 ± 0.37 c	4.22 ± 0.55 abc	1.449 *
Lymphocytes (1-4×10³/µl)	2.75 ± 0.19 ab	1.76 ± 0.18 b	3.38 ± 1.03 a	2.58 ± 0.20 ab	1.82 ± 0.14 b	1.50 ± 0.19 b	1.280 *
Monocytes (0.2-1×10³/µl)	0.413 ± 0.05 c	0.44 ± 0.07 c	0.786 ± 0.13 ab	0.966 ± 0.11 a	0.613 ± 0.05 bc	0.720 ± 0.11 ab	0.269 **
Eosinophils1 (0.1-0.5×10³/µl)	0.180 ± 0.02 a	0.120 ± 0.02 a	0.160 ± 0.04 a	0.186 ± 0.04 a	0.106 ± 0.02 a	0.10 ± 0.04 a	0.103 NS
Basophils (0.01-0.5×10³/µl)	0.146 ± 0.03 a	0.08 ± 0.01 b	0.073 ± 0.01 b	0.073 ± 0.01 b	0.053 ± 0.01 b	0.086 ± 0.01 b	0.056 *
Means having with the different letters in same row differed significantly. *(P≤0.05), **(P≤0.01), NS: Non-Significant.							

Table 4: Comparison Between Different Groups in Differential of WBCs.

Parameters	Mean + SE						LSD Value
	Control	Before	Treatment 1	Treatment 2	Treatment 3	Treatment 4	
Neutrophils (40-60%)	52.71 ± 1.58 bc	68.50 ± 3.13 a	56.21 ± 2.83 b	47.61 ± 1.50 c	58.12 ± 2.68 b	59.62 ± 4.39 b	8.05 **
Lymphocytes (20-40%)	35.28 ± 1.68 a	23.86 ± 2.25 b	31.46 ± 2.30 a	34.70 ± 1.37 a	29.32 ± 2.18 ab	30.37 ± 4.02 ab	6.89 **
Monocytes (2-10%)	6.10 ± 0.46 b	5.72 ± 0.72 b	10.43 ± 1.10 a	12.74 ± 0.75 a	10.25 ± 1.25 a	13.20 ± 2.05 a	3.31 **
Eosinophils (1-5%)	2.61 ± 0.23 a	1.94 ± 0.36 a	2.67 ± 0.77 a	1.98 ± 0.30 a	1.38 ± 0.21 a	1.78 ± 0.64 a	1.32 NS
Basophils (0.1-1%)	0.553 ± 0.10 c	0.833 ± 0.10 bc	0.906 ± 0.09 ab	1.213 ± 0.09 a	1.16 ± 0.11 a	1.013 ± 0.14 ab	0.309 **

Means having with the different letters in same row differed significantly. **($P \leq 0.01$), NS: Non-Significant.

Differential count of neutrophils decreased significantly ($P \leq 0.01$) in 1st, 2nd groups (56.21 ±2.83; 47.61 ±1.50) in comparison with before (68.50 ±3.13), 3rd (58.12 ±2.68), 4th (59.62 ±4.39). While before group was highly significant in comparison with control (52.71 ±1.58). Lymphocytes shows non-significant increase in four treated groups 1st, 2nd, 3rd and 4th (31.46 ±2.30; 34.70 ±1.37; 29.32 ±2.18; 29.32 ±2.18; 30.37 ±4.02) respectively. While before (23.86 ±2.25) shows significant decrease in comparison with control (35.28 ±1.68). Monocytes increased significantly ($P \leq 0.01$) in four treated groups (10.43 ±1.10; 12.74 ±0.75; 10.25 ±1.25; 13.20 ±2.05) when compared with before (5.72 ±0.72) and control groups (6.10 ±0.46). Eosinophil show non-significant difference in all cancer groups before; 1st, 2nd, 3rd and 4th (1.94 ±0.36; 2.67 ±0.77; 2.67 ±0.77; 1.38 ±0.21; 1.78 ±0.64) respectively in comparison with control groups (2.61 ±0.23). Basophils increased significantly ($P \leq 0.01$) in 1st, 2nd, 3rd, 4th (0.906 ±0.09; 1.213 ±0.09; 1.16 ±0.11; 1.013 ±0.14) in comparison with before and control groups (0.833 ±0.10; 0.553 ±0.10).

Discussion

Complete blood counts are regularly taken, as are other procedures for breast cancer, to test the amount of each type of blood cell circulating in the body. The complete blood count also helps test for different side effects of chemotherapy. In Present study, we found significantly low RBCs count and low levels of hemoglobin level in breast cancer patients as compared to normal healthy subjects. RBCs of patients affected by breast cancer are more sensitive to the denaturing action (Croci *et al*., 2002); (Radziwon *et al*., 2017). Anemia is the hematological abnormality that is most severe and recurrent in oncology patients (Van Belle and Cocquyt, 2003). Chemotherapy-induced anemia (CIA) is the result of malignant invasion of normal tissue resulting in blood loss, bone marrow infiltration with erythropoiesis disease and iron deficiency following inflammation (Henry, 1997). Low hemoglobin is associated with both adverse effects and decreased oxygenation of the tumour. Chronic anemia can be responsible for the lower case PCV. The anemia may be hemorrhagic and cause iron deficiency (Akinbami *et al*., 2013). Platelet counts were reduced in before and first treated groups although the values were within usual values although, Chauhan *et al*., 2016 recorded Platelet counts were increased as the treatment progressed from first chemotherapy to fifth chemotherapy phase. There are four blood platelet determinants used in clinical practice and they are useful in assessing pathological conditions (Roop *et al*., 2013) These are platelet counts, mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT). We observed that PDW and PCT increased respectively in the treated groups while MPV decreased in the fourth treated groups. For invasive breast cancer, the MPV pretreatment value is substantially higher than the value after treatment and its value is strongly correlated with the primary (Gu *et al*., 2015). The MCV were within normal range while MCH were lower as MCH = Hb × 10/RBC that HB was low in all breast groups and low RBCs in some groups which decreased in before, 1st and 2nd treated groups and MCHC were within normal values. The results were agree with that reported by Olufemi *et al*., 2013 in cross sectional study of age and variations of haematological parameters among female breast cancer patients and Total WBC in our study shows normal values while Akinbami *et al*., 2013. The mean WBC counts were recorded, the percentages of cases with neutrophils and lymphocytes were higher than the controls. This may be because of the association of neoplasms of all type linked with neutrophilia. Khan *et al*., 2017 results of WBC in the breast carcinoma patients are significantly reduced as matched to control. Beresford *et al*., 2006 identified

that Reduced blood count may result from chemotherapy and thrombocytopenia observed in many malignancies. Neutrophils were found to be high in groups before they were reduced in the fourth treated groups. agreed with reported by Chauhan *et al*., 2016 who found absolute leukocyte count was observed 5-6×10^9 /l neutrophils in average number of patients prior to initiation of chemotherapy courses. In the third and fourth group studied, the lymphocytes decreased as Chauhan *et al*., 2016 found total lymphocytes count was noted as 3.0 to 3.5×10^9 /l in majority of patients before chemotherapy. Our result agree with that recorded by Chauhan *et al*., 2016 who found monocytes count to be 0.6-0.7×10^9 /l before chemotherapy and 0.44 ±0.0710^3/µl in present study. No major difference, however, occurred during the first to fifth chemotherapy cycle. As the increase in values of our study were within normal values. Eosinophils showed no significant difference through verity courses of chemotherapy. Leukocytes, or white blood cells (WBCs), Are both immune and inflammatory processes involved. There are two main types of leukocytes: granular and a granular. Granular leukocytes include eosinophils, neutrophils and basophils, while a granular leukocytes are monocytes and lymphocytes, which lack cytoplasmic granules. Leukocytes generally play an important role in the immune response to macromolecules released from abnormal cells. Yoon *et al*., 2020. The percentage of neutrophils, lymphocytes and monocytes were significantly high in present study. Feng *et al*., 2011 reported that the percentage of monocytes highly increased in breast cancer patients. Hornychova *et al*., 2008 demonstrated that in immune system the monocytes and lymphocytes play a key role in response to inflammation and associated with several malignancies such as breast carcinoma. Eosinophilia is rare in healthy people; however, it is related to allergies, infections with helminths and certain inflammatory conditions. Eosinophilia is also found in colorectal, breast, ovarian, cervical, oral squamous cancer. As our results show non-significant difference but were high in 1st treated group while other groups were reduced. Basophils show an increase in 2nd, 3rd, 4th treated groups basophilia is usually occurs in patients with hematologic malignancies such as acute myelogenous leukemia, accelerated chronic myeloid leukemia and myelodysplastic syndrome. In conclusion, this study has shown that decreased RBCs and hemoglobin in all breast cancer groups after treated with chemotherapy that can cause anemia. And total leukocytes show non- significant difference While differential count of neutrophils, lymphocytes, monocytes and basophils increased among treated groups in comparison with control as affected by chemotherapy at various stages of treatments. The authors would like to thank the University of Mustansiriyah (www.uomustansiryiah.edu.iq) Baghdad-Iraq for its support in this work.

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