Effects of Adriamycin-Cytoxan Chemotherapy on Hematological and Biochemical profile among Breast Cancer Patients at Tertiary Care Teaching Hospital

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Abstract

Objectives: This study assessed the effects of chemotherapy on haematological and biochemical profile of breast cancer patients undergoing chemotherapy in the Tertiary Care Teaching Hospital. **Methods:** The study comprised sixty histopathological proven female breast cancer patients at Omega Cancer Hospital, GVPIHC & MT Teaching Hospital in Visakhapatnam. All subjects were divided into four groups: a control group of 60 healthy females of similar age, a group of 60 patients diagnosed with breast cancer and scheduled to start chemotherapy (treatment with anticancer agents) and recorded their demographic, clinical and therapeutic data. Blood was collected for biochemical analysis and for haematological profiles for day 1, day 21 and day 42 of their chemotherapy cycles. **Results:** Majority of the participants was within 30-75 years, married, overweight and had informal employment. The results showed that, there was a significant decrease in the mean values of haemoglobin, platelet count, neutrophile count and lymphocyte count during different successive cycles of treatment ($p<0.05$) but the TWBC count mean value was insignificantly variable during the successive cycles of anticancer treatment ($p>0.05$). The results were insignificant with Na+ and K+ ion concentration between the control and breast cancer individuals. From this study, we found that the parameters like AST, ALT, ALP, Urea, Creatinine and uric acid were significant biochemical markers in breast cancer patients. **Conclusion:** Chemotherapy produced significant adverse effects such as anaemia, neutropenia, leukopenia, thrombocytopenia, and hepatic dysfunction as a side effect of treatment due to disturbed levels of haematological and biochemical parameters.

Keywords

Breast cancer, AC (Adriamycin cyclophosphamide), oxidative stress, and chemotherapy/Treatment. Cancer, hematological profiles, biochemical profiles

Introduction

The most prevalent malignant tumour and one of the leading causes of cancer-related death in women is breast cancer [1-3]. Because of standard systemic therapy, such as chemotherapy, targeted therapy, endocrine therapy, radiotherapy, and numerous supportive treatments, the survival rates of breast cancer patients are rising. After receiving their initial diagnosis, 90% of breast cancer patients survive for at least 5 years [4]. Breast cancer symptoms include skin dimpling, breast tumours, breast shape alterations, fluid oozing from the nipple, and red,

scaly areas of skin [5]. The multifactorial aetiology of breast cancer comprises genetic, environmental, social, demographic, and hormonal variables. The existence of the disease as a result of elevated oxidative stress is supported by evidence. [6,7] Free radicals are highly reactive chemical entities that have an unpaired electron. They are created by the mitochondrial respiratory chain and the mixed function oxidase system in cells either as waste products of metabolism or during phagocytosis in the extra-nuclear compartment. These free radicals cause damage to the cellular structure like lipids, proteins and nucleic acids leading to severe abnormalities [8, 9]. Among all available anticancer medications, anthracyclines are among the best [10]. Depending on a wide range of variables, such as region, race, and ethnicity, there is a great deal of diversity in the clinical manifestation and genotype of this disease [11]. Chemotherapy is a crucial treatment for people with early-stage breast cancer because it increases overall and disease-free survival. Chemotherapy does, however, have long-term negative effects, such as CVD. Following chemotherapy, CVD (such as heart failure, myocardial ischemia, and hypertension) has become a frequent consequence [12, 13]. Eventually, some breast cancer patients pass away from other illnesses, particularly cardiovascular disease (CVD) [14]. The patients are at risk for a number of side effects, and these treatments are typically not curative. Anaemia, infection, bleeding issues, nausea, vomiting, allergic reactions, pain or discomfort, constipation or diarrhoea, hair loss, sore mouth, increased energy, and problems sleeping are a few side effects that might result from the usage of any cancer therapy. If this situation is not monitored properly, this may lead to treatment failure [15]. Haematological and biochemical profiles can be affected in a variety of ways by chemotherapy. Studies [16] have found that haematological measures are important prognostic indicators for evaluating the accuracy of risk stratification in breast cancer patients. To determine the levels of various components, the liver functioning (LFT) and kidney functioning (KFT) were evaluated in the current study. During chemotherapy, it assesses the condition and functionality of numerous organs. The liver function tests included measuring the levels of liver transaminases (AST, ALT) and alkaline phosphatase. As part of a kidney function test (KFT), blood samples are taken to quantify blood urea, creatinine, and uric acid [17]. Repeated chemotherapy alters biochemical profiles such as ALT, AST, alkaline phosphatase (ALP), urea, serum creatinine, and mineral ion concentrations and causes irreparable hepatocellular damage by attracting inflammatory cells. Similar to this, it has been demonstrated that chemotherapy can cause kidney cells to undergo apoptosis and necrosis. The clinical manifestation of this injury is an increase in urea and creatinine levels [18]. The kidney is also harmed by chemotherapeutic medicines. The nephron, which is the

kidney's functional unit, and its glomeruli, renal tubules, and inter-striatum are adversely damaged as serum creatinine concentration rises. Kidney damage resulted from this. The nephrotoxicity first exhibits no signs or symptoms before progressing to an imbalance in serum electrolytes. The body's urea and creatinine levels rise, causing short-term adverse effects include nausea and vomiting [19]. This study aimed to assess the effect of AC on hematological and biochemical parameters among BC patients at different intervals of treatment with normal subjects.

Materials and Methods

Study place

The study was conducted at Omega Cancer Hospital and Gayatri Vidya Parishad health care & medical technology at Visakhapatnam.

Study Design and Study Period

A retrospective study was conducted from March 2018 to July 2018 to compare hematological and biochemical profile changes in pre- and post-chemotherapy treatments of breast cancer patients admitted at the Oncology unit of Omega Cancer Hospital.

Study Population

Breast cancer patients started chemotherapy at the Oncology Unit of Omega Cancer Hospital, Gayatri Vidya Parishad health care & medical technology at Visakhapatnam from March 2017 to July 2018.

Inclusion Criteria

A total of 60 histopathological confirmed female patients with breast cancer who were given chemotherapy using the AC regimen (Adriamycin 60 mg/m2 and cyclophosphamide 600 mg/m2) were selected for the study. Before enrollment, each patient completed an informed consent form, and 60 patients did not get any chemotherapy. Three cycles day 1, day 21 and day 41 of their chemotherapy cycles days each with intravenous AC were administered to the patients. The study's control group, known as the unexposed group, was made up of participants who had not been exposed to radiation or chemicals and were clear of any malignant neoplasms as well as any clinical, biochemical, haematological, hepatic, or renal symptoms. At the time of diagnosis, the BC patients in our study had distant metastasis. We

assessed their clinic pathological characteristics, including histology, menopausal status, ER and PR status, number of affected axillary lymph nodes, grade, and tumour size and stage in accordance with the American Joint Committee on Cancer staging system. Medical records were consulted for information on clinical features, including cancer site, clinical stage, and HER-2/neu, ER (oestrogen receptor), and PR (progesterone receptor) status.

Exclusion Criteria

Breast Cancer patients who had incomplete medical records. Breast cancer patient who stopped their follow-up before completing the treatment for a cycle- IV. Patients who had other diseases and conditions that affect hematological and biochemical profiles.

Study Variables: Dependent Variable

White blood cells, red blood cells, hemoglobin, hematocrit, platelet, neutrophil, lymphocyte, urea, uric acid, creatinine, alanine aminotransferase, and aspartate aminotransferase, alkaline phosphatase. Total cholesterol, triglycerides, sodium, potassium & chlorides.

Independent Variable

Chemotherapy

Sample collection and preparation:

Peripheral blood sampling performed and after serum separation, the samples were immediately transported to the Biochemistry Research Laboratory and stored at -50^{o}C for biochemical tests.

Blood sampling:

7ml of fasting peripheral blood samples were collected from the Normal control group and patients. The separated serum was used to determine the levels of hematological parameters like white blood cell (TWBC) count, platelets (PLT), (hemoglobin (Hb), neutrophils and lymphocytes. First sampling performed 4 weeks after surgery (before the initiation of chemotherapy n=60 (C0), and second sampling at day 21 (usually, after 9 weeks from first chemotherapy (C2) and after 3 cycles of the intervention=60) and similarly followed by third sampling, (after intervention=60) (C4).

Evaluation of haematological parameters: The WHO reference range and the results of the CBC SYSMEX XK -21N hematology analyzer were used to determine whether specific hematologic abnormalities in haemoglobin (Hb), platelet count, total white blood cell count (TWBC), neutrophils, and lymphocytes were present. Biochemical parameters like estimation of Blood Urea was performed by Diacetyl Monoxime (DAM) method [20], Serum Creatinine by Jaffe's Method [21], Serum Uric Acid by Caraway's method [22], Serum Alkaline Phosphatase by King and Armstrong method [23] and Serum AST and ALT by Reitman and Frankel method [24-25]. The concentrations of Na+ and K+ ions were measured using Ion selective electrode method using a Sensacore electrolyte analyzer.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) 16.0 for Windows version was used to examine the data. The sociodemographic traits of the study subjects were then evaluated using a descriptive analysis. The mean±SD of various biochemical biomarkers, haematological indices, were compared using an independent sample t-test. The substantial variations in haematological parameters between patients and controls were also examined using a Chi-square test. Statistics were considered significant at P-values under 0.05.

Results

Total of 60 cases and 60 controls were included in this study. The mean ages of the study participants were 30-75 years (Table 1). The incidence of breast cancer was seen more in pre-menopause women (63.4%) than post-menopause women (Table 1). Majority of the cases were reported from urban area (60%). Most of breast cancer cases were reported in Ex-smoked individuals (46.6%). While observing the demographic variable like marital status most of the breast cancer patients were married women (63.4%). Majority of the breast cancer individuals had completed the primary education (23.4%) (Table 1). In reported cases of breast cancer individuals, the cancer site was mainly identified on the left side of the individuals (58.3%) (Table 2). Grade-1 clinical stage was seen in most of the cases (36.6%) and most of them were in metastasis stage (75%). The mean value of BMI was 24.22. Positive estrogen and progesterone receptors were seen in 65% individuals and negative estrogen and progesterone receptors were seen in 35% individuals (Table 2). Human epidermal growth factor receptor score +1 were seen in 38.3% breast cancer patients. By observing the clinical status, most of the patients have invasive ductal carcinoma (66.3%). Table 3 shows the comparison of various haematological variables between healthy

individuals and those with breast cancer over the course of various anticancer treatment cycles. The results showed that, there was a significant decrease in the mean values of haemoglobin, platelet count, neutrophile count and lymphocyte count during different successive cycles of treatment ($p<0.05$) but the TWBC count mean value was insignificantly variable during the successive cycles of anticancer treatment ($p>0.05$). Figure 1 showed the strong nuclear estrogen receptor (ER), strong nuclear progesterone receptor (PR) and uniform intense membrane HER2/neu and IHC Ki 67 immunoreactivity in tumor cells. Table 4 showed the comparative results of biochemical variables between control and breast cancer patients during first and second cycle of chemotherapy. The mean value of AST and ALT for control group was 30.26±7.30 and 27.36±5.77 whereas in breast cancer patients there was enhanced values of AST and ALT were identified before and after chemotherapy 80.550±13.45 and 92.83±19.73. The results were highly significant. There was a significant raise in the levels of ALP between the control groups 65.25±14.94 and in breast cancer patients after the first of chemotherapy 114.98±35.89 but the levels were declined after second cycle of chemotherapy 68.83±14.93. The mean value of serum urea and creatinine levels for control group was 25.20±6.21and 0.986±0.25whereas in breast cancer patients there was enhanced values of AST serum urea and creatinine were identified before and after chemotherapy 66.10±8.587and 5.140±1.32. The results were highly significant. The mean values of serum uric acid was enhanced after first cycle of chemotherapy 7.48±0.838 and later on decreased after second cycle of chemotherapy 4.96±0.765. The results were insignificant with Na+ and K+ ion concentration between the control and breast cancer individuals. From this study, we found that the parameters like AST, ALT, ALP, Urea, Creatinine and uric acid were significant biochemical markers in breast cancer patients.

Table 1: Demographic variables of the study population

Characteristics	**Control group**	**Breast cancer**
Total of patients	60	60
Age in years	30-75 years	30-75 years
Menopause [n (%)]		
Premenopausal	36(60%)	38(63.4%)
Postmenopausal	24(40%)	22(36.6%)
Residence		
Rural	38(63.4%)	24 (40%)

Urban	22 (36.6%)	36 (60%)
Family history of breast cancer [n (%)]		
Yes	6 (10%)	42(70%)
No	54 (90%)	18(30%)
Physical exercises [n (%)]		
Yes	28(46.6%)	18(30%)
No	32(53.4%)	42(70%)
Smoker [n (%)]		
Never smoked	35(58.3%)	11(18.3%)
Smoking	25(41.7%)	21(35.1%)
Ex-smoker	0%	28(46.6%)
Marital status [n (%)]		
Single	15(25%)	18(30%)
Married	22(36.6%)	38(63.4%)
Divorced	14(23.4%)	2(3.3%)
Widow	9(15%)	2(3.3%)
Education Level		
Not able to read and write	15(25%)	11(18.3%)
Able to read and write	11(18.3%)	13(26.75)
Primary education	16(26.6%)	14(23.4%)
Secondary education	10(16.6%)	10(16.6%)
College and University	8(13.3%)	9(15%)

Table 2: Clinical Characteristics of AC-Treated Control Group and Breast Cancer Patients

Characteristics	**Breast cancer patients number and %**
Cancer sites [n (%)]	
Left breast	35(58.3%)
Right mama	25(41.7%)
Clinical stage [n (%)]	

Grade 1	22(36.6%)
Grade 2	19 (31.6%)
Grade 3	19 (31.6%)
Metastasis, n (%)	
Yes	45(75%)
No	15(25%)
BMI, n (%)	
<18Kg/m^2	6 (10%)
18-24.5 Kg/m2	30 (50%)
25-29.5 Kg/m2	11 (18.3%)
30 Kg/m2	13 (21.7%)
BMI Mean value	24.22
BP	
SBP (mmHg) Mean value	118.9
DBP (mmHg) Mean value	78.6
Estrogen receptor [n (%)	
Negative	21(35%)
Positive	39(65%)
Progesterone receptor [n (%)]	
Negative	21(35%)
Positive	39(65%)
HER2/neu (human epidermal growth factor receptor) [n (%)]	
Score 0	11 (18.3%)
Score +1	23 (38.3%)
Score +2	13 (21.7%)
Score +3	13 (21.7%)
Clinical status	
Invasive ductal carcinoma	40(66.3%)
Invasive lobular carcinoma	11(18.3%)
Mucinous adenoCarcinoma	4(6.2%)
Medullary Carcinoma	3(6.2%)

Metaplastic carcinoma	1(1.5%)
Micropapillary carcinoma	1(1.5%)

Table 3: Comparison of haematological variables between control and breast cancer patients during first and second cycle of chemotherapy

Haematological Variables		Mean	SEM	SD	P-value
Haemoglobin	Control	12.1375	1.12105	.17725	0.01
	Before treatment	11.3800	1.05956	.16753	
	After first cycle of chemotherapy	10.3175	1.31459	.20785	
	After second cycle of chemotherapy	8.4550	.90948	.14380	
Platelet count	Control	3.5100	.38551	.06095	0.01
	Before treatment	3.4725	.44949	.07107	
	After first cycle of chemotherapy	2.5800	.64498	.10198	
	After second cycle of chemotherapy	2.4675	.62199	.09834	
TWBC	Control	10.0375	.61590	.09738	0.06
	Before treatment	10.9800	.85521	.13522	
	After first cycle of chemotherapy	10.0750	.76519	.12099	
	After second cycle of chemotherapy	9.3125	.84039	.13288	
Neutrophils	Control	56.1250	9.29623	1.46986	0.01
	Before treatment	59.6750	7.51200	1.18775	
	After first cycle of chemotherapy	55.7250	8.44587	1.33541	
	After second cycle of	51.6750	9.32707	1.47474	

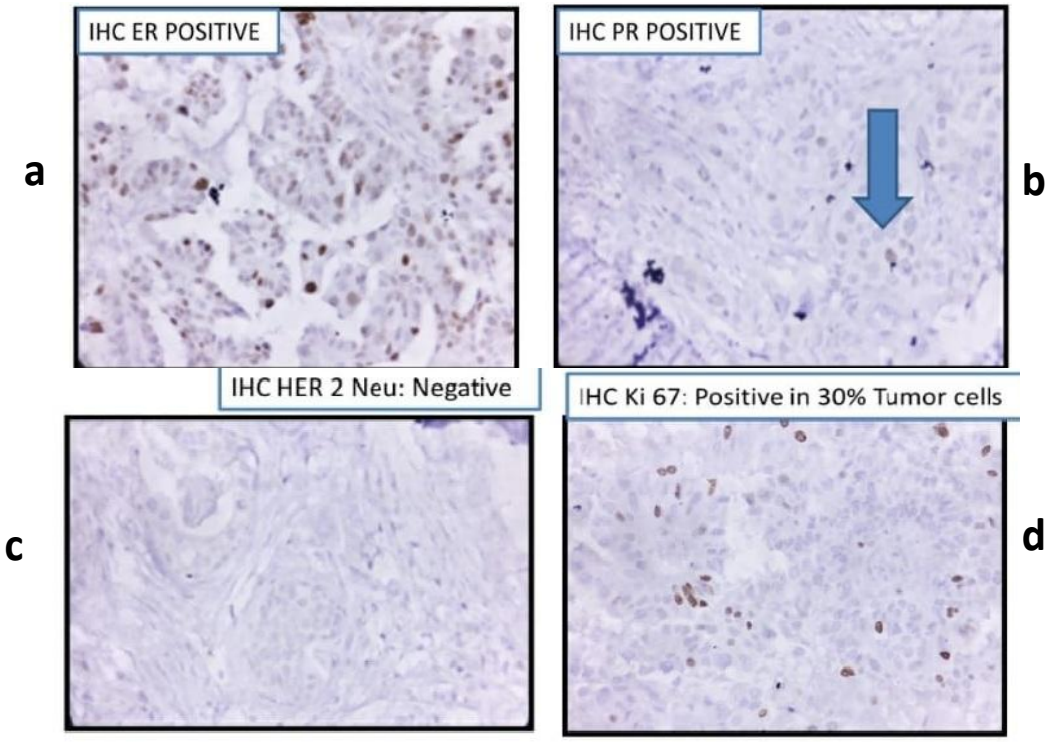
	chemotherapy				
Lymphocytes	Control	33.8750	7.73665	1.22327	0.02
	Before treatment	34.8750	7.71009	1.21907	
	After first cycle of chemotherapy	28.6000	7.30578	1.15514	
	After second cycle of chemotherapy	27.8500	6.48292	1.02504	

Table 4: Comparison of biochemical variables between control and breast cancer patients during first and second cycle of chemotherapy

Study population	**Biochemical parameters**	**Mean±SD**	**t-value**	**P-value**
Control	AST	30.26±7.30	**Paired 't' test by comparing control vs before chemo, after 1st and 2nd cycle of chemo**	
Before treatment		60.20±12.03	-17.444	.000
After first cycle of chemotherapy		63.90±12.82	-18.680	.000
After second cycle of chemotherapy		80.550±13.45	-26.061	.000
Control	ALT	27.36±5.77		
Before treatment		65.76±14.09	-20.732	.000
After first cycle of chemotherapy		66.48±13.42	-20.990	.000
After second cycle of chemotherapy		92.83±19.73	-24.974	.000
Control	ALP	65.25±14.94		
Before treatment		114.98±20.35	-13.224	.000
After first cycle of chemotherapy		114.98±35.89	-9.962	.000
After second cycle of chemotherapy		68.83±14.93	-2.166	0.034
Control	Urea	25.20±6.21		
Before treatment		58.33±10.15	-21.356	.000
After first cycle of chemotherapy		70.41±11.58	-25.837	.000
After second cycle of chemotherapy		66.10±8.587	-29.856	.000

Control	Serum creatinine	0.986±0.25		
Before treatment		3.93±0.55	-36.609	.000
After first cycle of chemotherapy		3.3933±0.92	-19.358	.000
After second cycle of chemotherapy		5.140±1.32	-23.552	.000
Control	Uric acid	4.96±0.75		
Before treatment		6.92±1.043	-11.650	.000
After first cycle of chemotherapy		7.48±0.838	-17.370	.000
After second cycle of chemotherapy		4.96±0.765	-.109	0.914
Control	Sodium ion concentration	136.8±3.077		
Before treatment		138.98±3.06	5.451	P<0.05
After first cycle of chemotherapy		134.9±3.19	6.566	
After second cycle of chemotherapy		132.83±2.44	11.392	
Control	Potassium ion concentration	3.84±0.25		
Before treatment		3.87±0.25	3.091	P<0.05
After first cycle of chemotherapy		3.870±0.25	3.091	
After second cycle of chemotherapy		3.701±0.288	4.072	

Figure 1. a-d: Photomicrograph showing strong nuclear estrogen receptor (ER), strong nuclear progesterone receptor (PR) and uniform intense membrane HER2/neu immunoreactivity in tumor cells.



Discussion

Chemotherapy is a cytotoxic drug that mainly works on the active cell. Chemotherapy is a cytotoxic drug that mainly works on the active cell. Active cells are those that are dividing and producing more of the same kind of cell. While some healthy cells, such as those in the blood and other organs, as well as cancer cells, are active, others are not. Chemotherapy destroys these healthy cells, which causes side effects [26]. For the treatment of BC, cyclophosphamide and doxorubicin (AC) are frequently combined [27, 28]. The cytochrome P450 system must convert the prodrug cyclophosphamide into active metabolites in order for it to stop malignant cells from dividing by cross-linking their DNA strands and reducing their DNA synthesis [29, 30]. There are few reports regarding haematological and biochemical profile changes in pre- and post-chemotherapy of cancer patients in the study area, despite several studies showing that enormous problems related to chemotherapy, especially on haematological and biochemical profile. However, some normal cells or non-targeted cells are also sensitive to this treatment and get damaged [31]. Intestinal toxicity and injury to the intestinal mucosa by AC chemotherapy can result in nausea, vomiting, mucositis, diarrhoea, and occasionally gastric reflux. Electrolyte imbalances, also known as dyselectrolytemias,

can result from persistent vomiting and diarrhoea. Serotonin is released by the GI tract's lining enterochromaffin cells, which causes chemotherapy-induced nausea [32]. Serotonin then activates 5-HT3 receptors in the GIT, the chemoreceptor trigger zone, and the nucleus tractussolitarius of the medulla oblongata, causing impulses to travel to the vomiting centre [32]. In the present investigation, the mean serum potassium level did not substantially rise in BC patients receiving AC. This runs counter to research that has already been done [33, 34]. This could be as a result of the study's smaller sample size. ALP is a sensitive indicator of both the progression of hepatocellular injury and minor biliary obstruction. Evidence has demonstrated that a significant portion of breast cancer patients with subsequent liver and/or bone metastases had abnormal ALP levels. In this study, patients' mean serum ALP levels before their first round of chemotherapy were higher than those in the control group, and they were also higher than those in the patients' serum levels after their second round of chemotherapy. These findings were significant. These outcomes were in line with the conclusions reached by Mohamad et al. in 2014 [35]. In a similar line, our work supports these conclusions on the detrimental effects of chemotherapy on haematological and biochemical parameters. Although not significantly, we saw that haemoglobin increased at the beginning of cycles and reduced following therapy. White blood cells (WBC), neutrophils, platelets, and lymphocytes all dropped after treatment. While after therapy, AST, ALT, and ALP increased. According to Warmkessel et al. 2011 [36], cyclophosphamide, an alkylating agent, causes nephrotoxicity by raising blood levels of urea and creatinine. The metabolic waste products of nausea and vomiting that build up in blood include urea and creatinine. The asymptomatic renal diseases were brought on by these increased levels. During the cycles, there are also noticeable changes in the blood urea creatinine and uric acid concentrations. Our findings demonstrated increased levels of the liver enzymes AST and ALT following AC-T treatment ($P<0.05$), supporting the use of serum levels of GOT and GPT as indicators of hepatic damage because intracellular enzymes are released into the blood during hepatic injury [37]. Comparisons between the mean serum GOT levels in this study were significant. When compared to the baseline levels of controls before and after therapy, breast cancer patients' serum GPT levels were considerably higher after treatment (P 0.05). Some studies [37, 38] found a significant increase in SGOT and SGPT blood levels ($P<0.05$) in breast cancer patients receiving chemotherapy. The chemotherapy (AC regimen), according to the current study, has a negative impact on the haematological and biochemical profile, leading to neutropenia, thrombocytopenia, anaemia, hyperuricemia, and liver

dysfunction [25]. In a similar line, our work supports these conclusions on the detrimental effects of chemotherapy on haematological and biochemical parameters.

Conclusion:

From this study, we found that the parameters like AST, ALT, ALP, Urea, Creatinine and uric acid were significant biochemical markers in breast cancer patients. Chemotherapy produced significant adverse effects such as anaemia, neutropenia, leukopenia, thrombocytopenia, and hepatic dysfunction as a side effect of treatment due to disturbed levels of haematological and biochemical parameters.

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Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRT, creatinine; DNA, deoxyribonucleic acid; Hb, hemoglobin; HCT, hematocrit; LDH, lactate dehydrogenase; LYM, lymphocytes; NUT, neutrophil; PLTs, platelets; RBCs, red blood cells; WBCs, white blood cells.

Consent for publication

The authors had taken the written informed consent from the patients.

Availability of data and materials

The authors declare that the data used in the present study were collected from the Omega Cancer Hospital, Visakhapatnam. The study doesn't use any licensed material or any previously published material. It is purely the authors' work.

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