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ORIGINAL RESEARCH

Blood cellular markers of inflammation in Breast Cancer and response to Neoadjuvant Chemotherapy

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Abstract

Background: Breast cancer is the most common female malignancy in Nigeria. Neoadjuvant chemotherapy is the first line treatment for locally advanced breast cancer. The advancement of many cancers is accompanied by inflammation, and inflammatory cells play an essential role in the progression.
Objective: To determine if haematological parameters can predict the responsiveness of breast cancer to neoadjuvant chemotherapy regime.
Method: A prospective cohort study of all breast cancer patients who had neoadjuvant chemotherapy between July 2017 and December 2018 was carried out. Haematological parameters of red cell count (RCC), white cell count(WCC), neutrophil count (NC), lymphocyte count (LC), platelet count (PC), red cell distribution width (RCDW), mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were measured. Response to chemotherapy was assessed by measuring the longest diameter of the lump and largest lymph node and applying the UICC criteria.
Results: Thirty-five females with breast cancer with the age range of 33-82 years and mean age of 48 ± 11 years were studied. The overall clinical response rate was 80% consisting of 40% complete clinical response, 40% partial clinical response, 8.6% stable disease and 11.4% progressive disease. Eleven (78.6%) with PLR values below average had good clinical response while 21.4% of those with PLR value above average had a good clinical response ($\chi^2 = 8.4$, $p = 0.006$)
Conclusion: The study showed that PLR is associated with complete clinical response to neoadjuvant chemotherapy and should be used as part of routine assessment before chemotherapy.

Keywords: Biomarkers, Blood cellular markers, Breast cancer, Neoadjuvant chemotherapy, Response rate.

Introduction

Breast cancer (BC) is the most common female malignancy in Sub-Saharan Africa and has a very high case fatality rate of 0.48 -0.55 compared with 0.15 in North America. [1] The incidence of BC is rising in low-income countries (LIC) and middle-income countries (MIC) but

not as high as in the high-income countries (HIC). [2] However, the mortality rate in BC in the HIC is much less than in the LIC and MIC. There are many reasons for this pattern of mortality in the HIC; these include an early presentation as a result of screening programs, adequate facilities for prompt diagnosis and affordable, effective treatment. [2] The situation is contrary in the LIC and MIC due to poor economic status, socio-cultural beliefs and practices which militate against early presentation and prompt treatment. [3] Therefore, BC patients in the LIC and MIC tend to present very late with attendant high mortality and morbidity. The majority of BC patients in sub-Saharan Africa, including Nigeria, present with locally advanced disease.

Neoadjuvant therapy has become the first line treatment for locally advanced breast cancer with numerous advantages, including a downstaging of the tumour. Therefore, breast conservation treatment is made feasible in a situation it was not initially possible and allows *in-vivo* observation of the effectiveness of the drugs in use. [4] Various studies have shown the varying degree of BC response to neoadjuvant chemotherapy, depending on the regime and the biological characteristics of the tumour. The grades of response according to the Union for International Cancer Control (UICC) method (include complete clinical response, partial clinical response, stable disease and progressive disease). [5]

Inflammation is involved in the growth and advancement of many cancers. Malignant changes occur at the sites of chronic irritation, inflammation, infection, and inflammatory cells play important roles in the development and progression of cancers. [6 - 8] Stimulated inflammation is involved in tumour invasion, growth, metastasis and angiogenesis. [9] Many inflammatory markers in the blood counts such as platelet, neutrophils and lymphocytes counts, neutrophil/lymphocytes ratio (NLR), platelet/lymphocyte ratios (PLR) and mean platelet volume (MPV) have been studied in patients with cancers. [10 - 12] Red cell distribution width (RDW) and platelet distribution width (PDW) have also been studied in the assessment of BC survival. [13] Lower survival rates have been observed in pre-treatment BC patients who had high NLR, PLR, and RDW.[14] MPV is a good prognostic marker in BC. [15] These routine haematological investigations are done as part of the initial evaluation of BC patients and be of prognostic importance. Therefore, examining their usefulness in predicting the responsiveness of BC to Adriamycin, Cyclophosphamide-Paclitaxel chemotherapy regime in use in our practice is essential.

The study aimed to determine the role of hematologic parameters (RBC, WBC, LC, PC, MPV, PDW, RDW, NLR, PLR) in predicting the responsiveness of BC to neoadjuvant chemotherapy (Adriamycin, Cyclophosphamide – Paclitaxel regime). We are not aware of any study which has examined this issue among Nigerian patients.

Methods

This was a prospective cohort study of all breast cancer patients presenting at the Breast, Endocrine and Oncology Unit of Surgery Department of the Olabisi Onabanjo University Teaching Hospital, Sagamu Nigeria, who received neoadjuvant chemotherapy as per the established unit protocol between 1st July 2017 and 31st December 2018.
Ethical clearance was obtained from the Health Research Ethics Committee of the hospital, and informed consent was obtained from all the study participants.

All patients with histologically confirmed breast cancer and palpable mass on neoadjuvant

chemotherapy who consented were included in the study. Patients with BC who declined consent, those with metastatic disease, those who are adjudged clinically unfit and those who declined neoadjuvant therapy were also excluded from the study.

The demographic characteristics, symptoms and duration of illness at presentation, menstrual status, findings on clinical examination including lump size (longest diameter measured with a calliper in centimetres), state of axillary lymph nodes (a measurement of the length of largest lymph node palpable in centimetres) were recorded., The clinical staging by Tumour Node Metastasis (TNM) method, histological type and grading, ER, PR and HER II receptors status were determined at the time of presentation before the commencement of therapy. Routine investigations to assess fitness to chemotherapy such as Full Blood Count (FBC), serum electrolytes and Urea (E&U), Electrocardiogram (ECG) and Chest X-ray were done at initial presentation. Full blood count consisting of red cell count (RCC), white blood cell count (WCC), neutrophil count (NC), lymphocyte count (LC), platelet count (PC), red cell distribution width (RDW), mean platelet volume (MPV) was performed using Symex nX-350 Automated Haematology Analyzer. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were calculated by dividing the values of NC and PC by the LC, respectively. Breast ultrasound was carried out in some patients to assess tumour size.

The regime of four courses of Adriamycin 60 mg/m2 and Cyclophosphamide 600mg/ m2 (AC) at three weekly intervals was followed by four courses of Paclitaxel 175mg/ m2 (P) at three weekly intervals was given with the standard precautions. [16] The routine investigations of FBC, E&U and LFT were carried out before each cycle of therapy.

The response to the therapy was assessed after the first dose and at the third dose each of the first line chemotherapy drug AC and P by measuring the longest diameter of the lump and length of the largest lymph node in centimetres and then applying the UICC criteria (complete clinical response, partial clinical response, stable disease, progressive disease). [5] Patients who showed progressive disease on this regime were referred to the Radiotherapist /Oncologist and were recognised as such. The side effects of the drugs observed were recorded. The regime described above was the unit protocol for managing BC using neoadjuvant therapy.

The data were collected on specially designed forms and were subsequently analysed with SPSS software version 20 using descriptive statistics such as means, standard deviations of continuous parameters (age, tumour size, RBC, WBC, LC, PC, MPV, PDW, RDW, NLR, PLR) while Chi-Square test was used to measure associations between categorical parameters and chemotherapy outcomes. A p-value <0.05 was considered statistically significant.

Results

Thirty-five female patients with BC were studied. The mean age was 48 ± 11years while the range was 33-82 years. Close to two-thirds (65.7%) were pre-menopausal, 62.9% were traders and 40.0% had education up to secondary school level as shown in Table I. The duration of symptoms ranged between 1 month and 24 months (mean 7.5 ± 6.5 months); the mean lump size was 11.3 ± 7.5cm with the range of 2-24cm. Table II shows that 29 (82.9%) had American Joint Committee on Cancer (AJCC) Stage III disease, All the patients had invasive ductal carcinoma and had between six to eight courses of chemotherapy of the AC-P regime.

Table I: Socio-demographic features of 35 patients with Breast Cancer

Features		Frequency	Percentage
Age group (Years)	≤ 40	10	28.6
	41-50	13	37.1
	51-60	9	25.7
	61-70	1	2.9
	>70	2	5.7
Menstrual status	Pre-menopausal	23	65.7
	Post-menopausal	12	34.3
Educational level	None formal	4	11.4
	Primary	5	14.3
	Secondary	14	40.0
	Tertiary	12	34.3
Occupation	Trading	22	62.9
	Civil service	4	11.4
	Teaching	4	11.4
	Artisans	2	5.7
	Unemployed	2	5.7
	Nursing	1	2.9

Table II. Tumour characteristics: AJCC stage and Immunohistochemistry

Characteristics		Frequency	Percentage
AJCC	I	2	5.7
	II	4	11.4
	III	29	82.9
Immunohistochemistry	TNBC	12	48.0
	Er+, Pr+, HER2+	3	12.0
	Er+, Pr+, HER2-	2	8.0
	Er-, Pr-, HER2+	7	28.0
	Er+, Pr-, HER2-	1	4.0

Er + Estrogen receptor Positive **Pr+ Progestogen receptor positive**
Er- Estrogen receptor Negative **Pr - Progestogen receptor negative**
HER2+ Human Epidermal Growth Factor Receptor 2 positive
HER2- Human Epidermal Growth Factor Receptor 2 negative
TNBC Triple Negative Breast Cancer.

The descriptive values of the haematological parameters, Haemoglobin (Hb), RBC, WBC, LC, PC, MPV, PDW, RDW, NLR, and PLR are shown in Table III.

The overall clinical response rate was 80.0%; this consisted of a complete clinical response in 40.0% and partial clinical response in 40.0%. Stable disease and progressive disease were observed in the remaining 8.6% and 11.4% respectively. The complete clinical response observed in 40.0% was classified as Good clinical response. On the other hand, the partial response observed in 40%, stable disease in 8.6% and progressive disease in 11.4% were jointly classified as Poor clinical response. The patients were then grouped into two groups based on the value of the haematological parameters (Hb, RBC, WBC, LC, PC, MPV, PDW, RDW, NLR, and PLR):

Table III: Blood parameters among patients with breast cancer

Parameter	Mean	Median	Mode	SD	Range
Red cell count (RCC) $x10^{12}/L$	4.3	4.3	4.2	.49	3.0-5.9
White cell count (WBC)$x10^9/L$	6.2	6.0	6.0	2.3	2.8-15.8
Lymphocyte count(LC)$x10^9/L$	2.1	1.9	1.9	0.9	.05-4.6
Platelet count(PLC)$x10^9/L$	288.5	251.0	204.0	155.1	120-1013
Mean Platelet Volume (MPV) ofL	10.3	10.5	10.3	1.3	6.0-12.1
Platelet Distribution Volume (PDV)	12.0	11.8	11.7	2.26	7.9-17.8
Red cell Distribution Width (RDW) 0fL	42.9	39.9	38.5	11.5	7.9-77.3
Neutrophil count (NC)$x10^9/L$	3.2	3.2	1.6	1.2	1.4-7.2
Neutrophil/Lymphocyte ratio(NLR)	1.7	1.4	1.2	0.7	0.6-3.9
Platelet/ lymphocyte ratio(PLR)	152	116	112.6	89.1	62-424
Haemoglobin (HB)	11.2	11.2	10.6	1.4	5.6-14.0

SD – Standard deviation

Group 1: As below average if the value of the parameter was less than the mean in case of a normally distributed variable or the median was used in those without normal distribution.
Group 2: Average and above if the value was equal or above the defined value. The comparison of complete clinical response and haematological parameters groups as defined above are shown in Table IV. Eleven patients (78.6%) with PLR in Group1 had good clinical response compared with 21.4% in PLR Group 2 patients. On the other hand, 71.4% of PLR Group 2 patients had poor clinical response compared with 28.6% of PLR Group 1patients (X^2 = 8.407, p = 0.006). There is no significant association between the other parameters and clinical response, as shown in Table IV. A cross-tabulation of PLR value against age, menstrual status, stage, tumour size and immunohistochemistry is depicted in Table V, but it shows no significant statistical association.

Discussion

The study population consisted of females with a mean age of 48 years, which is a decade earlier than the mean age for breast cancer among Caucasians. This finding agrees with the observation of other researchers. [16] The patients manifest evidence of late presentation such as long duration of symptoms and palpable lumps. This observation is expected since one of the criteria for inclusion in the study was a palpable lump as monitoring the lump size was the prime outcome measure.

The values of the haematological parameters were comparable to the previously observed values in breast cancer patients reported by Akanni *et al.* in Osogbo [17] and Akinbami *et al.* in Lagos [18] both of whom reported lower red cell parameters, higher white cell parameters and higher platelet parameters among breast cancer patients compared to the controls.

Table IV: Blood parameters and clinical response to neoadjuvant chemotherapy

Parameters		Poor clinical response		Good clinical response		Total		Statistics
		n	%	n	%	n	%	(χ^2, p)
Red Cell Count	Group 1	9	32.9	8	57.1	17	48.6	0.686, 0.500
	Group 2	12	51.7	6	42.9	18	51.4	
White Cell Count	Group 1	11	52.4	11	78.6	22	62.9	2.468, 0.162
	Group 2	10	47.6	3	21.4	13	37.1	
Lymphocyte Count	Group 1	14	66.7	8	57.1	22	62.9	0.326, 0.724
	Group 2	7	33.3	6	42.9	13	37.1	
Neutrophil Count	Group 1	13	61.9	6	42.9	19	54.3	1.288, 0.317
	Group 2	8	38.1	8	57.1	16	45.7	
Platelet Count	Group 1	9	42.9	8	57.1	17	48.6	0.686, 0.500
	Group 2	12	57.1	6	42.9	18	51.4	
Platelet Distribution Width	Group 1	10	47.6	8	57.1	18	51.4	0.305, 0.418
	Group 2	11	52.4	6	42.9	17	48.6	
Main Platelet Distribution Volume	Group 1	8	38.1	5	35.7	13	37.1	0.020, 1.00
	Group 2	13	61.9	9	64.3	22	62.9	
Neutrophil/Lymphocyte Ratio	Group 1	11	52.4	7	50.0	18	51.4	0.019, 1.00
	Group 2	10	47.6	7	50.0	17	48.6	
Platelet/Lymphocyte Ratio	Group 1	6	28.6	11	78.6	17	48.6	8.4, 0.006
	Group 2	15	71.4	3	21.4	18	51.4	
Red Cell Distribution Width	Group 1	12	57.1	6	42.9	18	51.4	0.686, 0.500
	Group 2	9	42.9	8	57.1	17	48.6	
Haemoglobin	Group 1	12	57.1	6	42.9	18	51.4	0.686, 0.500
	Group 2	9	42.9	8	57.1	17	48.6	

Low red cell indices imply anaemia which in the situation of malignancy can be attributed to bleeding from ulceration, nutritional deficiency from anorexia, bone marrow metastases with suppression of erythropoiesis and infection in the tumour leading to haemolysis. Of the haematological parameters studied, only PLR showed a significant association with good response to neoadjuvant therapy in which a good response was observed among 78.6% of Group 1 patients with PLR less than average (152).

Table V: Platelet Lymphocyte Ratio and age group, menstrual status, tumour size and immunohistochemistry

Parameters		PLR (Group 1)		PLR (Group 2)		Total		Statistics
		n	%	N	%	n	%	
Age	<40 years	6	35.3	4	22.8	10	28.6	0.417, 0.315
	≥40 years	11	64.7	14	77.2	25	71.4	
Menstrual status	Pre-menopausal	10	58.8	13	72.2	23	65.7	0.697, 0.489
	Post-menopausal	7	41.2	5	27.8	12	34.3	
Tumour size	<5 cm	8	47.1	3	16.7	11	31.4	3.7, 0.075
	> 5cm	9	52.9	15	83.3	24	68.6	
AJCC Stage	I and II	5	29.4	1	5.6	6	17.1	NC
	III	12	70.6	17	94.4	29	82.9	
Immunohistochemistry	TNBC	4	40.0	8	53.3	12	48.0	0.472, 0.404
	Non-TNBC	6	60.0	7	46.7	13	52.0	

TNBC – Triple Negative Breast Cancer **NC – Not Computed**

This observation is similar to the findings of Asano *et al*. who studied 177 breast cancer patients on neoadjuvant therapy of 5FU, Epirubicin, Cyclophosphamide regime followed by paclitaxel, and found that patients with low PLR had a higher pathological complete response rate. [19] Other workers like Rafee *et al*. [20] showed that higher PLR (> 138.19) was associated with poor response to neoadjuvant chemotherapy while Cuello-Lopez and colleagues demonstrated a better response to chemotherapy in the low PLR group. [21] Complete pathological response is a better measure of response to neoadjuvant chemotherapy than clinical response. However, it was not possible to study pathological response in this cohort as surgery was not done in some of them.

The observation of better response among patients with low PLR may be related to the fact that tumours have been shown to produce platelet factors which promote growth, invasion and metastasis, hence tumour activity may be measured by platelet count. [22] Chemotherapy agents cause thrombocytopaenia. It is observed that tumour suppression could be indicated by the presence of peripheral lymphocytosis with associated antitumour activity, especially of CD8+ T-cells. From the foregoing, it can be deduced that a BC patient with low PLR will have low platelet count, and a high lymphocyte count will display a high anti-tumour activity, better response to chemotherapy and overall more favourable prognosis.[19]

Various studies have shown a conflicting association between clinicopathological factors such as age, menstrual status, stage of the disease, tumour size and immunohistochemistry and PLR. However, in the present study, no association was observed between age, size, stage, and immunohistochemistry similar to the report of Cuello-Lopez *et al*. [21]

The relatively small sample size is acknowledged as a limitation as this limited the power of the study.

Conclusion

The present study suggests that, of all the haematological parameters studied, only PLR is associated with complete clinical response to neoadjuvant chemotherapy. Therefore, PLR

should be used as part of the routine pre-chemotherapy assessment of breast cancer patients.

Authors' Contributions: ABA, ABA, EHO, OTO, FOM and OKS participated in conception and design of the study, data analysis and interpretation. OKS, ABA, and EHO carried out the literature search, data interpretation and review. ABA, SBA, OTO and FOM drafted the manuscript. All the authors approved the final draft and made a substantial contribution to the intellectual content of the manuscript.

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