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Original Research Article

Expression of Some Inflammatory Biomarkers in Patients with Breast Cancer

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ABSTRACT

Introduction: Breast cancer is the commonest cause of cancer death in women worldwide. Breast cancer angiogenesis, is a key event in tumor genesis, invasion and metastasis. Tumor microenvironment is rich in inflammatory cells and survival markers that support their growth. There is increasing evidence that inflammatory cells may play a critical role in promoting tumor progression by producing various cytokines.
Aim: The aim of this study was to assess the levels of some inflammatory markers in patients with breast cancer compared to the levels of these markers in healthy female donors.
Method: Serum samples were collected from 58 breast cancer female patients (32 pre-treatment and 26 under chemo-radiotherapy) and 10 healthy female donors as controls. The levels of 7 inflammatory markers; Interleukin (IL)-1ß, IL- 6, IL-10, TNFα,MCP-1, G-CSF and Eotaxin were assessed by Bio-Plex Pro assays that quantify multiple protein biomarkers.
Results: There was a significant increase in IL-1ß (P = 0.001), IL- 6 (P = 0.01), IL-10 (P = 0.01), MCP-1 (P = 0.003), G-CSF (P = 0.001) and Eotaxin (P = 0.04) while an insignificant increase observed in TNFα (P = 0.08) in breast cancer pretreatment patients compared to controls. In patients under treatment there was a significant decrease in all biomarkers compared to those pretreatment as following; IL-1ß (P < 0.001), IL-6 (P < 0.001), IL-10 (P = 0.005), TNFα (P = 0.001), MCP-1 (P < 0.001), G-CSF (P < 0.001) and Eotaxin (P = 0.05). There is no significant difference in all markers levels in under treatment patients compared to controls.
Conclusions: Our results support an extended analysis of serum cytokine profiles for further development of serum screening assays potentially useful in diagnosis and staging of breast cancer. Furthermore, cytokine profiles may be useful for the immediate monitoring and evaluation of breast cancer treatment.

Key words: Breast cancer; Bioplex; IL-1ß; IL- 6; IL-10; TNFα; MCP-1; G-CSF; Eotaxin.

INTRODUCTION

Breast cancer has been defined as one of a heterogeneous group of related diseases which vary in natural history, risk markers, growth patterns and response to treatment. [1] It is expected that breast cancer will be newly diagnosed in over 1.5 million women each year, and that 500 000 women worldwide will die of this disease. While the incidence of new cases in some high income countries is stabilizing and death rates are falling, both appear to be increasing in developing counties. [2,3] The new cases mostly occur in women from low and middle income countries, in which the incidence is increasing by 5% per year and three

fourths of global breast cancer deaths occur. [4]

Biologically distinct entities subtypes of breast cancer have been identified using DNA microarrays by gene expression studies. [5] About 5-10% of breast cancer is thought to be linked to mutations in certain genes. BRCA 1 and BRCA 2 genes considered the most common of those genes. Women with BRCA 1 or BRCA 2 mutations have a high risk of developing breast cancer, ovarian cancer and several other types of cancer. [6] Estrogen receptor (ER) positive progesterone receptor (PR) negative tumors are a distinct subset of breast cancers identified by aggressive behavior. This subset of patients has greater expression of human epidermal growth marker receptor (HER)-1 and HER-2 and active GF signaling mediated by the phosphoinositide 3-kinase–Akt–mammalian target of rapamycin pathway. [7]

Advanced technology shifted toward assessing multiple markers rather than single one. One of those is Luminex multiplex technology, a recent advanced method in protein profiling. The advantage of this method is the marked efficiency in analyzing large number of markers with small analyzed volumes in significant reduced time. Multiplexing technology used for detection of multiple proteins such as cytokines, enzymes, and other antigens. [8] Infiltration of leukocytes was promoted by the immune system to eliminate or promote the development of breast cancer and tumor growth. [9,10]

Inflammation with or without a deregulated immune responses in the tumor microenvironment have been reported in many studies. Excessive Tamoxifen- resistant referred to inflammation-associated gene expression with [11]. In breast cancer, inflammatory signature and the immune response supports a theory that profile may provide useful information on patient prognosis and treatment. [12]

Cytokines are small polypeptides classified into two types: the pro- cytokine and the anti-inflammatory cytokines. The first type produced by 1 T-helper cells (Th1), and the second type is produced by 2 T-helper cells (Th2). Chemokines is another class of cytokine family that is responsible for chemotaxis of specific cells. Cytokines and chemokines are mostly associated with the presence of tumor. Assessment of multiple cytokine level is considered a global approach as a measure of the interaction between the immune system and the tumor for the diagnosis and/or prognosis of cancer patients. [13]

This study aimed to assess the levels of some inflammatory markers in serum of breast cancer female patients before start treatment and those under chemo-radiotherapy compared to the levels of these markers in serum of healthy female donors.

MATERIALS AND METHODS

The present work was conducted on 58 breast cancer (adenocarcinoma) female patients aged from 20 to 50 years. Patients were divided to 32 pre-treatment and 26 under chemo-radiotherapy after surgical treatment. Ten cases of those assessed before receiving any treatment were assessed also when they were under chemotherapy (<8 cycles) and added to the total number of under treatment patients.

The patients under treatment are subdivided into three groups (Group A: under treatment 1–4 cycles of chemotherapy, Group B: under treatment 5–8 cycles of chemotherapy and Group C: under treatment more than 8 cycles of chemotherapy and radiotherapy). Adjuvant therapy protocols given to breast cancer patients were; FAC (fluorouracil, Adriamycin, and Cytoxan), CMF (Cytoxan, methotrexate, and fluorouracil), or Arimedix, Tamofen, Tamoxofen or Taxotere. Ten apparently healthy female persons aged from 18 to 50 years old were subjected as controls .The levels of 7

inflammatory markers consisting of Interleukin (IL)-1ß, IL- 6, IL-10, tumor necrotic factor-alpha (TNFα), monocyte chemoattractant protein-1 (MCP-1), granulocyte-colony stimulating factor (G-CSF) and Eotaxin were assessed from EDTA-blood samples from all patients and controls using Bio-Plex Pro assays (Cat. #M50007W214, Bio-Rad, USA) that quantify multiple protein biofactors.

The Bio-Plex® system instruction is formed from the following elements:

1) Fluorescently dyed microspheres (beads), each of them has distinct code or addressed spectra. This instruction making detection of different types of molecules in the same well of those 96- well.
2) A flow-cytometer for dedication and to measure the different molecules bound to the surface of the beads through two lasers associated with optics.
3) A digital signal processor with high-speed that manages the fluorescence data efficiently.

Data was statistically analyzed through SPSS (Statistical Package for Social Sciences) (Standard version release 20.0). Descriptive statistics in the form of mean (±SD) for quantitative data that presented as mean ± standard deviation. Test for normal distribution of data was used. Independent t test was used to compare between two different means.

Mann Whitney was used to compare between 2 continuous variables. Paired t test was used to compare means in same group before and after treatment $P \leq 0.05$ was considered as the level of statistical significance. Accuracy of studied markers was performed by ROC curve and the correlation between these factors was analyzed by Pearson test.

RESULTS

Regarding the same 10 cases of breast cancer (before and under treatment), it was found from (Table 1) that most of inflammatory markers were significantly higher before starting treatment compared to controls as; IL-1β ($P_1 < 0.001$), IL-6 ($P_1 = 0.009$), IL-10 ($P_1 = 0.006$), MCP ($P_1 = 0.002$), G-CSF ($P_1 < 0.001$) and Eotaxin ($P_1 = 0.04$) while TNF-α was insignificantly increased ($P_1 = 0.11$). In those patients who were under chemotherapy treatment (< 8 cycles), there were significant decrease in the levels of IL-1β ($P_2 < 0.001$), IL-6 ($P_2 < 0.001$), IL-10 ($P_2 = 0.002$), TNF-α ($P_2 = 0.004$) G-CSF ($P_2 < 0.001$) compared to their levels before start treatment but insignificant decrease of MCP ($P_2 = 0.08$), Eotaxin ($P_2 = 0.11$). There were insignificant differences between the levels of all studied inflammatory markers in patients under chemotherapy compared to controls ($P_3 > 0.05$).

Table (1): Inflammatory markers levels in same cases with breast cancer before and under treatment compared to controls.

Markers	Cases mean: pg/ml (± SD)			Significance P- value		
	Control (N: 10)	Pre-treatment (N: 10)	Under treat (<8 cycles) (N: 10)	P_1	P_2	P_3
IL-1β	1.6 (± 0.4)	2.7 (± 0.7)	1.4 (± 0.4)	< 0.001	< 0.001	0.3
IL-6	6.7 (± 3.6)	11.2 (± 3.3)	5.3 (± 2.7)	0.009	< 0.001	0.34
IL-10	5.2 (± 3.1)	9.8 (± 3.5)	4.8 (± 2.6)	0.006	0.002	0.8
TNF-α	9.3 (± 4.6)	12.9 (± 4.9)	6.5 (± 3.5)	0.11	0.004	0.14
MCP-1	5.4 (± 2.7)	13.9 (± 6.9)	8.7 (± 5.5)	0.002	0.08	0.11
G-CSF	32.7 (± 14.7)	75.5 (± 24.1)	33.6 (± 21.5)	< 0.001	< 0.001	0.9
Eotaxin	14.9 (± 11.3)	42.3 (± 37.9)	20.6 (± 15.3)	0.04	0.11	0.4

P_1: Pre-treatment versus controls. (t-test), P_2: Pre-treatment versus under treatment. (t-test)
P_3: Pre-treatment versus controls. (t-test)

Table (2): Assessment of serum levels of the inflammatory markers in pre-treatment and under treatment total cases breast cancer in comparison to controls.

Markers	Cases mean: pg/ml (± SD)		Significance P- value			
	Control (N: 10)	Pre-treatment (N: 32)	Under treatment (N: 36)	P_1	P_2	P_3
IL-1β	1.6 (± 0.4)	2.8 (± 1.0)	1.5 (± 0.7)	0.001	< 0.001	0.4
IL-6	6.7 (± 3.6)	12.7 (± 7.8)	6.4 (± 3.8)	0.01	< 0.001	0.7
IL-10	5.2 (± 3.1)	10.3 (± 6.9)	6.3 (± 4.8)	0.01	0.005	0.7
TNF-α	9.3 (± 4.6)	13.0 (± 7.4)	7.6 (± 4.8)	0.08	0.001	0.16
MCP-1	5.4 (± 2.7)	11.6 (± 7.4)	6.0 (± 4.1)	0.003	< 0.001	0.9
G-CSF	32.7 (± 14.7)	67.2 (± 37.8)	36.3 (± 22.2)	0.001	< 0.001	0.8
Eotaxin	14.9 (± 11.3)	30.1 (± 25.7)	19.5 (± 12.0)	0.04	0.05	0.3

P_1: Pre-treatment versus Controls. (Mann-Whitney Test), P_2: Pre-treatment versus Under treatment. (Mann-Whitney Test)
P_3: Under treatment versus Controls. (Mann-Whitney Test)

The (Table 2) identified inflammatory markers levels of in the breast cancer patients before treatment (32 cases) compared to their levels in the total cases under treatment (36 cases). Inflammatory markers levels were significantly higher in pretreatment patients compared to controls; IL-1ß (P_1 = 0.001), IL- 6 (P_1 = 0.01), IL-10 (P_1 = 0.01), MCP-1 (P_1 = 0.003), G-CSF (P_1 = 0.001) and Eotaxin (P_1 = 0.04) while an insignificant increase observed in TNFα (P_1 = 0.08). All markers were significantly lower in patients under chemo-radiotherapy compared to pretreatment as, IL-1β, IL-6, TNF-α, MCP, G-CSF (P_2 < 0.001 for each), IL-10 (P_2 = 0.005) and Eotaxin (P_2 = 0.05). Studied inflammatory markers levels reviled insignificant difference in under treatment patients compared to controls (P_3 > 0.05).

These studied markers were analyzed through ROC curve to determine their accuracy in diagnosis of breast cancer. It show that most markers were moderately accurate (AUC = 0.6 – 0.7) while TNF-α show poor accuracy (AUC = 0.508) as in Fig. 1 and table 3.

The correlations between studied markers were performed by Pearson test (Table 4). It was found that a good positive correlation between IL1B and most other markers (r > 0.7) while weak positive correlation with MCP (r = 0.617) and Eotaxin (r = 0.382). IL6 show Good positive correlation with IL1B (r = 0.759) and G-CSF (r = 0.77) while weak positive correlation with others (r < 0.7). IL10 had good positive correlation with IL1B, TNF-α and G-CSF. There was good positive correlation between TNF-α and IL1B, IL 10 and G-CSF (r > 0.7). Eotaxin show very weak positive correlation with all other markers (r < 0.7).

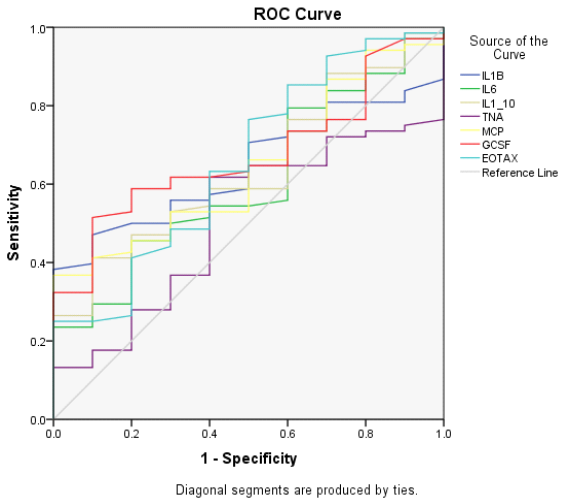

Figure (1): ROC curve of inflammatory markers

Table (3): Interpretation of accuracy of inflammatory markers according to ROC curve

Area Under the Curve (AUC)				
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
IL-1β	0.643	0.067	0.512	0.775
IL-6	0.607	0.086	0.439	0.775
IL-10	0.639	0.081	0.479	0.798
TNF-α	0.508	0.085	0.341	0.675
MCP-1	0.646	0.078	0.494	0.799
G-CSF	0.674	0.072	0.533	0.816
Eotaxin	0.657	0.093	0.475	0.838
Good accuracy if AUC ≥ 0.5				

Table (4): Correlation between studied inflammatory markers in patients with breast cancer

Correlations								
		IL1B	**IL6**	**IL 10**	**TNF**	**MCP**	**GCSF**	**EOTAX**
IL-1B	Pearson Correlation (r)	1.000	0.759**	0.712**	0.716**	0.617**	0.756**	0.382**
	Sig. (2-tailed) *(P)*	.	0.000	0.000	0.000	0.000	0.000	0.001
IL-6	Pearson Correlation (r)	0.759**	1.000	0.687**	0.610**	0.523**	0.770**	0.445**
	Sig. (2-tailed) *(P)*	0.000	.	0.000	0.000	0.000	.000	0.000
IL- 10	Pearson Correlation (r)	0.712**	0.687**	1.000	0.781**	0.487**	0.762**	0.603**
	Sig. (2-tailed) *(P)*	0.000	0.000	.	0.000	0.000	0.000	0.000
TNF-α	Pearson Correlation (r)	0.716**	0.610**	0.781**	1.000	0.470**	0.762**	0.611**
	Sig. (2-tailed) *(P)*	0.000	0.000	0.000	.	0.000	0.000	0.000
MCP-1	Pearson Correlation (r)	0.617**	0.523**	0.487**	0.470**	1.000	0.614**	0.464**
	Sig. (2-tailed) *(P)*	0.000	0.000	0.000	0.000	.	0.000	0.000
G-CSF	Pearson Correlation (r)	0.756**	0.770**	0.762**	0.762**	0.614**	1.000	0.557**
	Sig. (2-tailed) *(P)*	0.000	0.000	0.000	0.000	0.000	.	0.000
Eotaxin	Pearson Correlation (r)	0.382**	0.445**	0.603**	0.611**	0.464**	0.557**	1.000
	Sig. (2-tailed) *(P)*	0.001	0.000	0.000	0.000	0.000	0.000	.

**. Correlation is significant at the 0.01 level (2-tailed).
r = 0.5 – 0.6 (weak positive correlation) - r = 0.7 (good positive correlation)
r = 0.8 – 0.9 (strong positive correlation)

When the total cases under treatment were divided into three groups; Group (A): cases under treatment (1–4) cycles of chemotherapy, Group (B): cases under treatment (5–8) cycles of chemotherapy and Group (C): cases under treatment more than 8 cycles of chemotherapy and radiotherapy. A comparative study was done to compare the levels of inflammatory markers in serum of patients in these groups to their levels before start treatment and to those of controls (Fig 2). As regard group (A) the following markers were significantly lower than pre treatment patients, IL-1β, IL-6, IL-10 (P_2 = 0.002, 0.01 and 0.04 respectively) but others were insignificantly lower (P_2 > 0.05). Group (B) shows significant lower levels in most of markers compared to pretreatment patients IL-1β (P_3 < 0.001), IL-6 (P_3= 0.002), TNF-α (P_3 = 0.02) MCP (P_3 = 0.001) and G-CSF (P_3 <0.001) while IL-10 and Eotaxin were insignificantly lower (P_3 > 0.05). In group (C), inflammatory markers were significantly lower than pretreatment patients (P_4 < 0.05) except MCP-1 and Eotaxin (P_4 = 0.1 and 0.5 respectively). It was observed that the levels of all inflammatory markers were insignificantly different in patients under treatment compared to controls ($P_{5,6,7}$ > 0.5).

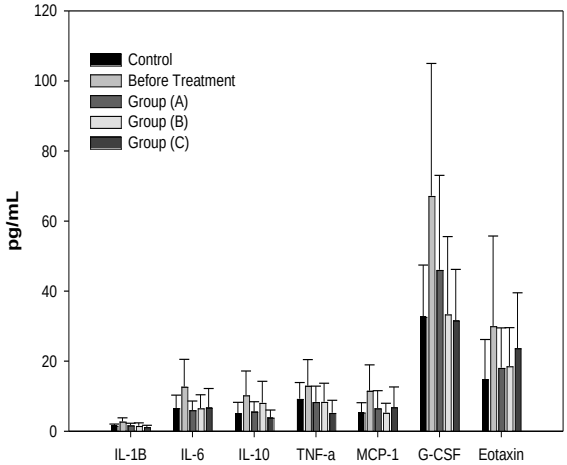

Figure (2): Inflammatory markers in breast cancer patients before treatment, Group A, Group B, Group C and controls.

DISCUSION

Breast cancer is a complicated disease accounting for 26% of all female cancers. The risk of breast cancer development related to family history increases with the number of affected relatives, specific lineage and age at diagnosis. The younger the age at diagnosis, the more likely a genetic component may be involved. [6] There are other many markers that influence breast cancer development and progression with hormone and nuclear receptors playing critical roles. Several reviews explain the roles of estrogen and nuclear receptors in breast cancer. [14]

Inflammation within the tumor microenvironment correlates with increased invasiveness and poor prognosis in breast cancer. During different stages of

tumor development the immune system can either identify and destroy tumor s, or promote their growth. [15]

In this study some inflammatory markers as; IL-1ß, IL- 6, IL-10, TNFα, MCP-1, G-CSF and Eotaxin were assessed using Bio-Plex Pro assays technique in plasma of breast cancer female patients before start treatment and those under chemo-radiotherapy after surgical procedure compared to the levels of these markers in healthy female donors.

Our results reported a statistically significant elevated level of studied inflammatory markers at pretreatment patients with breast cancer compared to controls ($P_1 < 0.05$) except TNF-α which insignificantly increased ($P_1 = 0.11$). When these patients received chemo-radiotherapy, these markers were significantly decreased compared to pretreatment except MCP-1 and Eotaxin (P_2= 0.08 and 0.11 respectively). All seven markers show statistically insignificant differences in these patients who received chemo-radiotherapy compared to controls ($P_3 > 0.05$).

Also a comparative study was done between the levels of inflammatory markers in breast cancer patients before treatment and others under chemo-radiotherapy compared to controls. It was found a statistically significant increase of the markers levels compared to controls ($P_1 < 0.05$) except TNF-α ($P_1 = 0.08$). Patients under chemo-radiotherapy show significant lower markers levels compared to pretreatment as; IL-10 ($P_2 = 0.005$), Eotaxin ($P_2 = 0.05$) and statistically highly significant decrease in IL-1β, IL-6, TNF-β, MCP-1 and G-CSF ($P_2 < 0.001$ each). All markers in patients under chemo-radiotherapy show statistically insignificant differences than controls ($P_3 > 0.05$).

On dividing patients under chemo-radiotherapy into groups, it was found a significant decrease in most markers levels with increasing cycles of chemo-radiotherapy.

Immune system is the controller of tumor future. It has the ability to prevent or promote tumor growth. This process is comprised of three phases: elimination, equilibrium and escape. [9] Elimination is achieved through the nascent transformed cell destruction by acute tumor-inhibiting inflammation. It characterized by infiltration of effectors cells of the innate and adaptive immune system and the production of tumor- inhibiting cytokines. The escape phase is sustained by chronic tumor- promoting inflammation that mainly involves immunosuppressive cells and soluble markers. [16] Evading immune destruction has been recognized as a hallmark of cancer. [17] Breast carcinomas are heavily infiltrated by different types of host leukocytes; primarily T cells, and monocytes that differentiate into tumor-associated macrophages (TAM) at the tumor site. Breast cancers could be eliminated or promoted to develop by these leukocytes. Tumor cells were accepted widely to induce a suppressive microenvironment that supports tumor growth. That suppressive micro-environment is comprised of immuno-suppressive cells and soluble markers. [18]

In breast tumors, the mainly immunosuppressive cells that have been identified were; regulatory T (Treg) cells (a potent negative regulator of the antitumor immune response) and myeloid-derived suppressor (which is a heterogeneous population of cells of myeloid origin that expand during cancer inflammation and infection cells (MDSCs). The MDSCs induced by many markers that include GM-CSF, PGE2, IL-6, stem cell marker (SCF) and VEGF. [19] Interleukin-10 (IL-10) is a pleiotropic anti-inflammatory cytokine that induces immunosuppression and assists in escape from tumor immune surveillance. IL-10, like several other cytokines, also can exert dual proliferative and inhibitory effect on breast tumor cells indicating a complex role of IL-10 in breast cancer initiation and progression. [20]

The main types of inflammation in tumorigenesis and cancer include: chronic inflammation that precedes tumor development, tumor- associated inflammation and therapy-induced inflammation. [21]

The most highly reported inflammatory cytokine in breast cancer is Tumor necrosis factor alpha (TNF-α). TNF-α has a cytotoxic and apoptotic activities reported on breast tumor cell lines. TNF-α function is also depends on many other multiple markers, such as estrogen treatment and epidermal growth marker. [22] Activity of TNF-α correlated with many different physiological conditions. Cell-type-dependent manner contributes to a sense of ambiguity regarding its antitumor effects. [23] TNF-α serum concentration reported higher significant correlation with more progressed tumor phenotypes patients. TAM-derived TNF-α expression was suggested to play an important role in the metastases of breast cancer. Also, elevated levels of IL-6 may contribute to disease progression. Interleukin (IL)-1β indicated that its levels were significantly higher in invasive carcinoma than in ductal carcinoma *in situ* or in benign lesions, implying that elevated levels of IL-1β are directly correlated with a more advanced disease. [24] Of interest is the fact that the two cytokines (IL-6 and IL-1) and TNF-α are three cytokines form a network of related markers that may affect tumor cell progression in a cooperative manner interrelated and may act in an additive manner. [25,26]

The presence of multiple areas of hypoxia is a common feature of solid tumors. Many markers produced in hypoxia, such as monocyte chemotactic protein-1 (MCP-1), granulocyte-macrophage colony-stimulating marker (GMCSF) and Eotaxin, are potent chemokines chemotactic toward the monocytes in nearby blood vessels. [27]

Tumor-infiltrating monocytes (TAM) may be stimulated by chemokines to secrete protumorigenic markers. Also, these inflammatory cytokines may act not only on the inflammatory cells, but also by specific chemokine receptors that are expressed by these cells directly on the tumor cells. [28] G-CSF mobilizes CD34-positive cells into peripheral blood. Recent studies have demonstrated that circulating CD34+/Flk-1^{+} cell can differentiate into Eothelial cells and augment neovascularization which promotes tumor growth. [29] Eotaxin (CCL11) is a potent chemoattractant for eosinophils, basophils, Th2 lymphocytes, human microvascular endothelial cells and also it induces the formation of blood vessels in vivo. The angiogenic response induced by eotaxin was about one-half of that induced by basic fibroblast marker, and it was accompanied by an inflammatory infiltrate, which consisted predominantly of eosinophils. [30] MCP-1, eotaxin and GM-CSF levels were significantly elevated in breast cancer ($P < 0.009$) [13]

Prospective studies have shown prolonged deficits in certain lymphocyte populations especially naïve CD4 T among breast cancer patients treated with radiation and chemotherapy. [31] Methotrexate, an anti-metabolite that inhibits the synthesis of purine and pyrimidine precursors, appears to have anti-inflammatory properties. Specifically, methotrexate can inhibit growth of monocytes and macrophages cells which can produce the cytokines and chemokines. [32] Cytoxan decreases the level of immunosuppressive cytokines, such as TGF-B and IL-10 and stimulates the recovery of IFN-gamma-producing natural killer T cells, stimulates the maturation of dendritic cells, and maintains the survival of memory T cells. [33]

CONCLUSION

Our data show the significant increase in the levels of some inflammatory markers as IL-1ß, IL- 6, IL-10, MCP-1 and G-CSF but there is an insignificant increase in levels of TNFα and Eotaxin in breast cancer patients before starting treatment. On other hand the data show a significant decrease in the levels of all biomarkers in breast cancer patients under treatment. Understanding the inflammatory pathways in breast cancer may lead to the development of new drugs specifically targeting this system and less toxic than ordinary drugs.

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