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Estimation of Interleukin-10 and Interleukin-22 levels in the advances of breast cancer

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Abstract

Background: Breast cancer is the secant kind of carcinoma in women with higher incidence in Iraq. There are many prognostic and predictive factors used for management of the breast cancer. Serum levels of the cytokines may be utilized as a marker of immunity status and prognosis in CA breast.

Aims of the Study: Measuring the cytokines (IL-10 and IL-22) in breast cancer patients and association between the cytokines (IL-10 and IL-22 with stage and grade for breast cancer patient.

Materials and Methods: The case control study was conducted on 60 females with CA. Breast and 60 healthy controls group, the age both groups between 31-70 year, Groups patients with CA. Breast were referred to Middle Euphrates cancer center in Najaf and private the clinics for Physicians Oncology during the period November 2019 -October 2020. Measurement of cytokines (Interleukin-10 and Interleukin-22) by using Enzyme Linked Immunosorbent Assay.

Results: The showed a levels of IL-10 (186.3 ±39.5 pg/L) and IL-22 (187.1 ± 54.7ng/L) in patients of breast cancer higher than IL-10 (91.8 ± 30.6 pg/L) and IL-22 (82.6 ± 28.7 ng/L) in healthy control, and showed a high levels of IL-22 in advances stage and grade III. The showed non-significant in levels of IL-10 between four stages and three grade.

Conclusion: A significant elevation levels of IL-10 and IL-22 in breast cancer women groups comparison with control group, elevation significant of immunological levels of IL-22 in stages and grades of breast cancer women.

Keywords: IL-10; IL-22; Breast Cancer; ELISA.

1. Introduction

Breast cancer is a form of malignancy caused by abnormal growth and unregulated division of cells within the terminal and lobular units of the breast that can infiltrate and kill the surrounding normal tissue. As well as spread across the body by blood or lymph fluid to new locations (1, 2). It is the most frequent malignant disease and the leading cause of death from cancer among women worldwide (3). Breast cancer is the most common cancer for women around the world, accounting for 25% of all cases (4). In 2018 it resulted in two million new cases and 627,000 deaths (5). Breast cancer division splits breast cancer into divisions based on a variety of factors that has a specific reason. The histopathological type, tumour grade, tumour stage, and protein and gene expression are the most important categories (6). As the cells lose the characteristics found in typical breast cells, pathologists identify them as well differentiated

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(low-grade), moderately differentiated (intermediate-grade) and poorly differentiated (high-grade).Cancers that are poorly differentiated have a poor prognosis (7,8). The current breast cancer staging schemes are dependent on the clinical size and degree of invasion of the primary tumour (T), the clinical absence or presence of palpable axillary lymph nodes and signs of local invasion (N), as well as clinical and imaging proof of distant metastases (M) (9).

IL-10 is produced by TH0, TH2, cytotoxic T cells, Treg, γδ-T cells, NK cells, NK T cells, B cells, dendritic cells, eosinophils, mast cells, and activated monocytes. It was originally known as the cytokine synthesis inhibitory factor because of its capacity to inhibit the production of certain cytokines. In general, IL-10 is the most studied and well-known anti-inflammatory cytokine (10). Interleukin-10 that plays an important coordinated role in breast cancer (11), which regulates immune response (12) and inhibits pro-inflammatory roles of Antigen-Presenting Cells (APCs) by expressing antagonizing costimulatory molecules. Its low expression is linked with poor survival outcome (13).

Interleukin-22 is a type of cytokine that has alpha-helical structure. IL-22 binds to a cell surface receptor that is composed of two subunits: IL-10R2 and IL-22R1 (14). Elevated expression of IL-22 has been observed in many human tumours, including ovarian, breast, hepatocellular, esophageal, gastric, and non-melanoma skin cancers (15). However, anticancer effects of IL-22 have been reported in cancer, where it slows cancer cell growth by arresting the G2/M cell cycle, resulting in reduced cell proliferation and tumour weight (16). There was also a good positive association with IL-22, linked to a high SBR grade. That IL22 was upregulated in the serum and tissues of BC patients and that this was linked to clinical stages (17).

2. Material and methods

The case-control study was conducted on 60 females with CA. Breast (breast cancer) and 60 healthy controls group, the age both groups between 31-70 year, Groups patients with CA. Breast were referred to Middle Euphrates cancer center in Najaf and private the clinics for Physicians Oncology during the period November 2019 - October 2020. Some information were gathered from each woman such as the governorate, grade and stage and according to a questionnaire sheet prepared previously. The distribution of patients according to these criteria was shown in (Table 1).

Table 1 Breast cancer patients and the criteria used in this study

Criteria	No. of CA Breast patients (60)
Tumor stage	
I	12
II	19
III	18
IV	11
Histological grade	
G1	17
G2	25
G3	18

2.1. Preparation of serum samples and ELISA detection of cytokines

5 ml of blood samples were taken from redial vein of each woman by using disposable syringes. Then, the tube was centrifuged at 3000 rounds per minute (rpm) for 10 minutes to collect the serum. The obtained serum was avoid repeated freezing and thawing of samples which is not recommended because this may affect the quality of the results. All sera were stored at -20℃ for future immunological analysis. Measurement of cytokines (Interleukin-10 and Interleukin-22) by using Enzyme Linked Immunosorbent Assay Kit (Bioassay Technology Laboratory-China).

2.2. Statistical Analysis

This study was a type of case-control study. The statistical significance was done by using SPSS (Statistical Package for Social Sciences) version 17 computer software for the analysis purpose of the data. The ANOVA test was used to determine the statistical significance of the difference in mean between more than two groups. Z- Test was also used to

find out statistical significance of differences between two independent variables means. P value less than the 0.05 level of significance was considered statistically significant (18).

3. Results

3.1. Mensuration Mean of IL-10 and IL-22 in the Groups

The present results revealed high significant differences (P<0.001) in mean of IL-10 in patients of breast cancer group was (186.3 ±39.5pg/L) compared with healthy control group was (91.8 ± 30.6 pg/L). In addition to that showed high significant differences (P<0.001) in mean of IL-22 in patients group was (187.1 ±54.7 ng/L) compared with healthy control group was (82.6 ± 28.7 ng/L) as shown Table (2).

Table 2 Comparison the mean levels of IL-10 and levels of IL-22 according to between groups

Interleukins	Breast Cancer Group	Healthy Control Group	P - value
IL-10 pg/L M ± SD	*186.3 ±39.5	91.8 ± 30.6	0.0001
IL-22 ng/L M ± SD	*187.1 ± 54.7	82.6 ± 28.7	0.0001

M: mean, SD: standard deviation

3.2. Evaluation of mean levels of IL-10 and IL-22 in the studying groups according to Cancer Stages

In regard to the tumor stages, there no significant differences in mean of IL-10 between in stages patient of CA. Breast group. The highest significant differences(P<0.01) in mean of IL-22 patients of breast cancer group compared between stages in group, the highest IL-22 levels in stage II, III and IV was(181.1 ± 48.1 ng/L, 195.3 ± 44.9 ng/L and 239 ± 41 ng/L respectively) than in stage I was(137.6 ± 49.1 ng/L), the mean of IL-22 levels was higher in advance stages (stage IV and stage III) of breast cancer as shown Table (3).

Table 3 The IL-10 and IL-22 mean levels in different stages of CA. Breast patients

Stages	IL-10 pg/L M ± SD	IL-22 ng/L M ± SD
Stage I	180.3 ± 34	137.6 ± 49.1
Stage II	176.5 ± 42	*181.1 ± 48.1
Stage III	193.3 ± 28.5	**195.3 ± 44.9
Stage IV	198.3 ± 54.1	***239 ± 41
LSD	11.8	17.9
P - value	0.396NS	0.00012

LSD: Least Significant Differences,*(P<0.05), ** (P<0.01), *** (P<0.001), NS: no significant

3.3. Evaluation of mean levels of IL-10 and IL-22 in the studying groups according to Cancer Grades

Table 4 The IL-10 and IL-22 mean levels in different grades of CA. Breast patients

Grades	IL-10 pg/L M ± SD	IL-22 ng/L M ± SD
Grade I	174.5 ± 40.1	151.4 ± 57.4
Grade II	189 ± 32.8	*196.2 ± 45
Grade III	193.6 ± 46.9	**208.2 ± 50.5
LSD	12.6	14.3
P - value	0.332NS	0.0005

LSD: Least Significant Differences,*(P<0.01), ** (P<0.001), NS: no significant

According to the grade status, in Table (4) showed that there no significant differences in mean titer of IL-10 was shown in patient's breast cancer group compared between three grades. Furthermore, the mean of IL-22 in breast cancer in grades (G1, G2 and G3) was (151.4 ± 57.4, 196.2 ± 45 and 208.2 ± 50.5 ng/L) respectively with statistically significant differences (P<0.01) when compared between grades.

4. Discussion

Cancer is a major cause of death in economically developed countries and in developing countries, which is the second major cause of death (19). Cancer-related deaths are projected to increase worldwide, with 11 million deaths expected by 2030 (20). Despite the fact that this malignant has a good prognosis, it was the most frequent cause of cancer-related death (21).

Interleukin-10 is a pleiotropic anti-inflammatory cytokine that causes immunosuppression and assists tumour immune surveillance escape. IL-10 has a dual proliferative and inhibitory effect on breast tumour cells, indicating a complex role for IL-10 in the initiation and progression of breast cancer (22). Anti-inflammatory cytokines play an important role in tumour development; for example, IL-10, a potential anti-inflammatory cytokine, stimulates the forming of a microenvironment that suppresses anti-tumor immune responses and promotes cancer cell growth (22, 23). The result of study demonstrated a highly significant P-value (<0.01) increase level of IL-10 in breast cancer women in comparison with control group. The result of study agreed with study by Abeer, who found increase level of IL-10 in breast cancer women in comparison with control group (24), this is agrees with Kozlowski et al. that found a strong relationship between the concentration of IL-10 and breast cancer, where levels of interleukin 10 in the serum of women with breast cancer were statistically higher than in control (25).

Interleukin 22 (IL-22) is upregulated in a variety of human cancers, and several studies have shown that IL-22 plays a tumor-supporting role in the growth of these cancers (26). IL-22 has been shown to stimulate epithelial cell proliferation, transformation, and migration in breast cancer (17, 27.28, 29). This study showed high significant differences in mean level of IL-22 between patients of breast cancer groups and control groups. The results of study agreed with results in Tunisia, the found high level of IL-22 in patients of breast cancer (30). However, the few studies which reported tumour suppressive effects of IL-22 were generally carried out over a period of time in a non-physiological environment with exogenous IL-22 injections, and cannot necessarily reflect the natural role of the endogenous host IL-22 in tumorigenesis modulation (31, 32). Given that commensal microbial elements have recently been associated with inflammation mediated tumour development (33), it can affect the understanding of whether IL-22 plays a role directly or indirectly in tumour promotion, especially at tissue sites where epithelial-microbiotic interactions are intense (34). IL-22 also has key a role on cancers that arise from non-mucosal sites such as the breast or prostate, as well as its effects on metastases (35).

Cancer is typically diagnosed at a late stage, where the prognosis is low and the efficacy of therapy is limited. Furthermore, there are problems with distinguishing four stages, including the TNM classification (9). Thus, there is a huge opportunity to improve cancer patients' outcomes by enhancing diagnosis and care approaches, as well as ongoing research and assessment of biomarkers in relation to therapeutic efficacy and overall survival (36). The results in the study that demonstrated the no significantly difference (P>0.05) levels of IL-10 with tumor stages in patients of breast cancer. The results agreed with study in Baghdad-Iraq, who found no correlation of IL-10 level with stages of breast cancer (24), other the study in China, found no significant differences in IL-10 levels between I, II and III stages of breast cancer (37). These results were consistent with those reported that IL-10 levels in gastric cancer patients were not correlated to tumour stage38). Those results were incompatible with those reported in China, reported a significantly increase in serum IL-10 levels in patients with TNM stage II and III ductal carcinoma than in stage I ductal cancer (P<0.001) in malignant breast diseases (39). In certain epithelial cancers, such as breast and lung cancer, the role of IL-22 in cancer progression has been recognized. When immune cells release IL-22, it can promote tumour growth, aggressiveness, and treatment resistance by acting on cancer cells (26, 40). The results in the study that demonstrated the significantly difference (P<0.01) levels of IL-22 with tumor stages in patients of breast cancer. Other study showed IL-22 absenteeism in TME during initiation and hyperplasia stages of breast cancer. It was expressed in the early stages of carcinoma and increased significantly as the tumour advanced to the malignant stage (41). Another research observed that the IL-22 levels in stage III-IV patients were significantly higher than in stage I-II in RCC patients (42). The current understanding of IL-22 function is dependent on advanced-stage cancer cell line models in which IL-22 has been shown to promote cell proliferation, transformation, and migration in human and mouse cancer cell lines (17, 27,

29). IL-22 and HOXB-AS5 were shown to to upregulated in the serum and tissues of BC patients and were linked with clinical stages of the cancer (43).

Breast tumours are classified into grade I (G1; well-differentiated, slow-growing), grade II (G2; moderately differentiated), and grade III (G3; poorly differentiated, highly proliferative) (44). IL-10 is essential for the suppression of pro-tumor inflammation mediators (45); however, IL-10 may have a potential role in tumour angiogenesis regulation (46). The results in the study that demonstrated the no significantly difference ($P>0.05$) levels of IL-10 with tumor grade in patients of breast cancer. The results agreed with a study by Abeer, no found the association of IL-10 level with grades of breast cancer (24). The complex role of IL-10 in determining the immune response seems to be influenced by the tissue microenvironment and the expression of IL-10 receptors on different immune cells (45). The results in the study that demonstrated the higher significantly difference ($P<0.01$) levels of IL-22 with tumor grades in patients of breast cancer. The results agreed with study in Tunisia, found the high level of IL-22 was significantly associated with a high histopathological grade (Grade III) (47). Some recent studies have indicated elevated IL-22 level was correlated with breast cancer progression (28). In the tumour tissue, IL-1 and IL-23 increased the production of IL-22.Thus, IL-1 and IL-23 promoting breast cancer progression via IL-22 be one possible mechanism (48).

5. Conclusion

A significant elevation levels of IL-10 and IL-22 in breast cancer women groups' comparison with control group that showed the importance of these cytokines to promote or suppress immunity toward breast cancer. Elevation significant of immunological levels of IL-22 in breast cancer women groups were also shown in patients with an advanced stage and grade III of breast cancer, which may be considered as a non-invasive primitive marker for earlier prediction of breast cancer staging and grading.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest is exist.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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