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Estimation of Serum CD200 and CD200R1 Levels in a Sample of Iraqi Women with Breast Cancer: Their Role as Diagnostic and Prognostic Markers

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Abstract

Breast cancer is a disease in which cells in the breast grow out of control. CD200 is a cell surface glycoprotein expressed on many cells, it belongs to the immunoglobulin family (Ig) and have a great role in the regulation of inflammation in autoimmunity. CD200 is the ligand for CD200R1 receptor. To determine if serum level of CD200 and its receptor CD200R1 can be used as a diagnostic and prognostic marker in patients with breast cancer.This case control study was carried out at Oncology Teaching Hospital – Medical city in Baghdad. Six groups were enrolled, four groups were confirmed with breast cancer stage (I, II, III and IV), fifth group (benign) and sixth group was control (healthy individual). Serum is divided to measure CD200 and CD200R1 by utilizing quantitative sandwich enzyme-linked immunosorbent assay (ELISA) Kits.

Serum level of CD200 was significantly different (P=0.000088) between breast cancer patients and control only, serum level of CD200 increases with disease stage and there is a significant positive correlation. Serum level of CD200R1 was different with stage, although the differences were not significant but the level of CD200R1 is lower in stage 4 patients than other stages.

Serum CD200 level can be used as a diagnostic marker for breast cancer. Serum level of CD200R1 can be used as a prognostic marker.

Keywords: CD200, CD200R1, Breast cancer, Serum CD200.

قياس مستوى سي دي ٢٠٠ و مستقبل الـ سي دي ٢٠٠ في المصل لعينة من النساء العراقيات المصابات بسرطان الثدي: بيان دورهما كمؤشرات في التشخيص و المتابعة

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الخلاصة

سرطان الثدي هو مرض ينتج عن نمو خلايا الثدي بصورة غير طبيعية. كتلة التمايز(CD٢٠٠) هو بروتين سكري يظهر على العديد من الخلايا في الجسم، ينتمي ال CD200 ينتمي الى عائلة الجلوبيولين المناعي وله دور كبير جدا في تنظيم الالتهاب في حالة الامراض المناعية. CD200 هو المحفز الخاص للمستقبل CD200R1.

تهدف هذه الدراسة الى امكانية استخدام مستويات الـ CD200 و المستقبل الخاص بهCD200R1 في تشخيص و متابعة تقادم المرض في مرضى سرطان الثدي.

اجريت هذه الدراسة في مستشفى الاورام التعليمي – مدينة الطب في بغداد .تتكون هذه الدراسة من ٦ مجموعات، تم توزيع المرضى المصابين بسرطان الثدي على اربع مجموعات ، المجموعة الأولى (المرحلةالأولى) ، (المجموعة الثانية (المرحلة الثانية) ، المجموعة الثالثة (المرحلة الثالثة)، المجموعة الرابعة (المرحلة الرابعة)، المجموعة الخامسة (حميدة) و مجموعة السيطرة (المتطوعين الأصحاء). تم فصل المصل الذي وتقسيمه إلى عدة اقسام لقياس CD200 و CD200R1 باستخدام الفحص المناعي الكميELISA quantitative . كانت الاختلافات في مستويات مصل الدم من الـ CD200 ذات دلالة إحصائية جيدة (P=0.000088) بين مرضى سرطان الثدي و المتطوعين الاصحاء فقط، مستويات الـ CD200 تزداد مع زيادة مرحلة المرض كما يوجد ارتباط إيجابي بينهم. كانت مستويات CD200R1 مختلفة، على الرغم من ان الفوارق لم تكن كبيرة لكن هذه المستويات كانت اقل ما تكون لدى المرضى في المراحل المتقدمة من سرطان الثدي.

يمكن استخدام الـ CD200 كمعلّم تشخيصي حالات سرطان الثدي، كما يمكن استخدام الـ CD200R1 لمتابعة تقادم المرض.

الكلمات المفتاحية: كتلة التمايز ٢٠٠ (CD200)، المستقبل الخاص بكتلة التمايز CD2001R1، زيادة مستويات CD200.

Introduction

Cancer is the second cause of death worldwide; about 17 million new cases of cancer were diagnosed in 2018. High mortality rate is also associated with breast cancer as it comes fifth 627000 deaths annually. According to the global cancer observery in 2018, the number of new cancer cases for both sexes of all ages in Iraq was 25,023 case, breast cancer was the highest number of cancers 5,141 (20.3%) followed by lung cancer 2,123 (8.4%). The number of deaths was 2,060 (14.2%) from lung cancer and 1,727 (11.9%) from breast cancer[(1)].

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Breast cancer (BC) can be divided histologically into invasive and non-invasive, ductal carcinoma in situ is the common type of non-invasive, while common type of the invasive are invasive lobular and invasive ductal carcinoma [(2)]. Molecular classification ; as two types, luminal A in which there is an expression of estrogen receptor, progesterone receptor without human epidermal growth factor receptor-2, and luminal B in which there is estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 not over-expressed [(3)]. Metastasis is a complicated pathological process; it begins with increased cell motility and cell migration then stromal invasion. Subsequently, tumor cells intravasate into blood vessels and/or lymphatic system; they survive in the circulation; then extravasate, colonize in distant organs, and finally, sometimes after several years of dormancy, grow to overt metastases [(4)]. CD200 is a cell surface glycoprotein expressed on many cells, it belongs to the immunoglobulin family and have great role in the regulation of inflammation in autoimmunity, organ transplantation and viral infections [(5)]. CD200 is the ligand for CD200 receptor (CD200R), which is a receptor with an immune inhibitory activity expressed on myeloid and lymphoid cells and is considered an immunological checkpoint [(6)]. Multiple studies have been documented the tumor-promoting effects of CD200 in leukemia [(7)], there are opposing results regarding its role in solid tumor. CD200 expression is associated with increased metastatic survival of squamous cell carcinoma [(8)]. In different circumstances, expression of CD200 by melanocytes results in reduced incidence of lung metastasis, and CD200R activation by an agonistic monoclonal antibody (OX110) is associated with decreased CD200-negative melanoma tumor formation in the lungs [(9)]. If it is not expressed on the primary tumor, CD200 can be induced on the tumor during its progression, which supports a function as enhancer of tumor cell survival. For example, metastatic squamous cell carcinomas (SCC) gain CD200 expression both in mice and men by same way during progression of the tumor [(8)]. CD200R1 is belong to the Ig superfamily transmembrane glycoprotein found on the surface of myeloid cells. CD200R1 interacts with its ligand CD200, which is also belongs to the Ig superfamily transmembrane glycoprotein, which down regulate myeloid cell functions. CD200 is expressed on the surface of a variety of cells including neurons, epithelial cells, endothelial cells, fibroblasts, lymphoid cells, and astrocytes [(10)]. CD200R-signaling increases the threshold for immune activation and is known to be highly important for restraining inflammatory responses, while CD200 expression on tumor cells is a marker for disease progression, suggesting a role in suppression of anti-tumor responses [(11)]. This study carried out to determine if serum level of CD200 and its receptor CD200R1 can be used as a diagnostic and prognostic marker in patients with breast cancer.

Materials and Methods

Subjects

This case control study was carried out over the 7 months period from April 2019 until November 2019 at Oncology Teaching Hospital – Medical city in Baghdad. A total number of eighty-four participants enrolled (patients and apparently healthy volunteers) in this study, they diagnosed by physician based on the histopathology analysis and mammography. Ethical approval was obtained from Ethics Committee – Ministry of health.

Patient selection

Fifty-six women with confirmed breast cancer were participated in the study with mean age (47.8 ±11.98 years). The diagnosis of cancer was confirmed by histopathology analyses and mammography Dr. Weam Abdulfatah and Dr. Ahmed Hussein [(12)]. Those patients were newly diagnosed and those on chemotherapy.

Participants are grouped as six groups, group 1: 14 women with stage I BC, group 2: 14 women with stage II BC, group 3: 14 women with stage III BC, group 4: 14 women with stage IV BC, group 5: 14 women with benign breast tumor, and group 6: 14 healthy women.

Data collection

All Participants completed interview-administered questionnaires regarding family history of breast cancer and other malignancies, medical history, reproductive history, and breast feeding.

Other information's were collected from hospital records to determine cancer stage, hormonal receptor status and treatment protocol, the following data were obtained:

- Histopathological report and histological classification of cancer.
- Molecular classification of cancer.
- Age at diagnosis
- Chemotherapy status
- Tumor type, size, and grade.
- Lymph Node Status.

Blood sample collection

Venous blood specimen (5 ml) was withdrawn from each woman and placed in gel-containing tubes, left at room temperature for at least 1 hour for clotting, the specimens then centrifuged at 3000 rpm for 8 minutes. The obtained serum was separated and divided into aliquots (which kept frozen at -80°C until their assay) to measure CD200 and CD200R1.

Laboratory analysis

Reagent Preparation for CD200 and CD200R1

A. Wash Buffer:

Aliquots of 750ml diluted washing buffer were prepared by adding 30 ml of the concentrated buffer to 720 mL of distilled water.

B. Standard for CD200:

To prepare 8000 pg/ml of standard solution: 1 ml Sample / Standard dilution buffer added into one Standard tube, from this tube a serious of dilutions are made to get the required concentrations as follow (4000, 2000, 1000, 500, 250, 125 pg/ml) respectively.

C. Standard for CD200R1:

To prepare 50 ng/ml of standard solution: 1 ml Sample / Standard dilution buffer added into one Standard tube, from this tube a serious of dilutions are made to get the required concentrations as follow (25, 12.5, 6.25, 3.13, 1.57, 0.78 ng/ml) respectively.

D. Preparation of Biotin-labelled Antibody Working Solution

According to the manufacturer, Biotin-labeled antibody were freshly prepared by diluting the antibody with the dilution buffer at 1:100 ratio.

E. Preparation of HRP-Streptavidin Conjugate (SABC) Working Solution:

This solution prepared within 30 minutes before experiment. SABC diluted with SABC dilution buffer at 1:100 and mix them thoroughly.

Measurement of Serum CD200 Level

Serum CD200 level was estimated using a ready-made kit (Elabscince ®) an Enzyme-Linked Immune Sorbent Assay (ELISA) for CD200 (OX-2 membrane glycoprotein) is Sandwich-type (quantitative) assay using two specific antibodies, first one anti-CD200 antibody was pre-coated onto microtiter plate provided in the kit and the second one biotin-conjugated anti-CD200 antibody was used as a detection antibody. The concentration of CD200 in the samples is then determined by comparing the optical density of the samples to the standard curve.

Measurement of Serum CD200R1

Serum CD200R1 level was estimated using (Elabscince®) an Enzyme-Linked Immune Sorbent Assay (ELISA) for CD200R1 (CD200 Receptor 1) which is a quantitative Sandwich-Assay using provided plate pre-coated with anti-CD200R1 antibody. The concentration of CD200 in the samples is then determined by comparing the optical density of the samples to the standard curve. The results were expressed as (ng/ml).

Statistical Analysis

Statistical package for social sciences version 25 (SPSS v. 25) was used for data input and analysis.

Analysis of Variance (one-way): to determine the difference in means of 3 independent samples, followed by Tukey's test (post-hoc test) to identify significantly different means among the groups.

Sensitivity and specificity test and receiver operating characteristic (ROC) to determine the sensitivity and specificity of the data.

Pearson's correlation coefficient (r): to evaluate the correlation between the parameters. Results with ($P<0.05$) were considered to be significant.

Results

The mean of serum CD200 concentration were significantly higher in breast cancer patients and in benign tumor than in control (apparently healthy) group, and the differences in the mean was highly significant with P value <0.05 Table (1). Analysis of variance (ANOVA) for breast cancer stages show no significant differences in the mean of CD200 concentration with p value of (0.665) Table (1).

Table 1. Serum CD200 concentrations and significance for control, benign and stages of BC women.

Study groups	N	Serum CD200 level (pg/ml)	Standard Error
Control	14	347.40[b]	34.86
Benign	14	776.44[ab]	98.31
Stage 1	14	939.36[a]	97.15
Stage 2	14	1025.74[a]	118.43
Stage 3	14	1046.04[a]	128.04
Stage 4	14	1181.19[a]	189.65
p-value for all groups			0.000088*
P value for cancer stages			0.665

*Highly significant (P<0.01)

Superscripts (a,b) refer to statically significant differences

The correlation between breast cancer stages and serum CD200 concentration is positive medium (r = 0.545), as breast cancer stage progresses, the level of CD200 increases and this correlation becomes significant (P=0.00002) Table (2).

Table 2. Serum CD200 concentration correlation and significance with stages

Correlations		
		CD200 concentration
Stage	Correlation	0.450**
	Sig.	0.00002

** Correlation is significant at the 0.01 level (2-tailed).

Sensitivity and specificity at different serum concentrations is shown in the Table (3), the best cut-off point is at the concentration of (533.18 pg/ml) that shows (88%) sensitivity and (100%) specificity. Area under the curve for breast cancer compared to control is (0.948) which is very high

and is highly significant as in Table (4). Better illustration of ROC curve showed in the figure (1).

Table 3. Sensitivity and specificity of CD200 concentration for BC women vs. control

CD200 concentration (pg/ml)	Sensitivity %	Specificity %
324.5	98	50
380.68	96.4	64.3
462.9	89.3	71.6
509.17	89	85.7
533.18	88	100
567.5	87.5	100

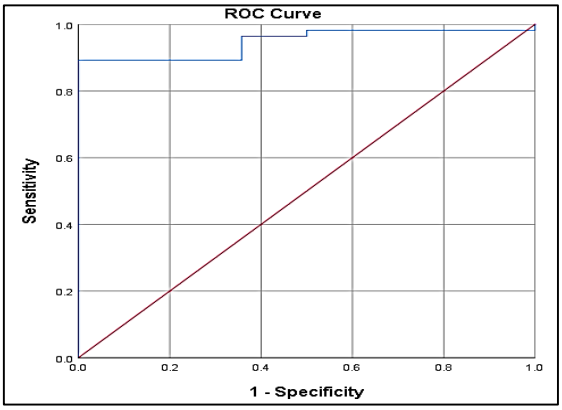

Figure 1. ROC curve for serum CD200 for BC women vs. control

Table 4. Area under the curve for breast cancer women vs. control

Area	Std. Error	Asymptotic Sig.
0.948	0.026	0.00001*

* Highly significant (P<0.01)

The highest serum level of CD200R1 seen in stage 2 patients, while stage four had the lowest, stage one and three show nearly equal levels, as in the Table (5).

Although the level of CD200R1 is different among the groups, but it was statistically not significant (P=0.293) Table (5),

Table 5. Serum CD200R1 concentration for control, benign and stages of BC women

Group	N	Serum CD200R1 level (ng/ml)	Standard Error
Control	14	36.923	6.41
Benign	14	60.211	28.04
Stage 1	14	78.783	18.02
Stage 2	14	97.372	39.75
Stage 3	14	71.699	30.39
Stage 4	14	22.437	2.61
P-value			0.293

Sensitivity and specificity of serum CD200R1 level for stage 4 compared to other stages which represents the best cut-off points are shown in Table (6) below;

Table 6. Sensitivity and specificity of CD200 for stage 4 BC compared to other stages

Stages compared to stage 4	CD200R1 concentration (ng/ml)	Sensitivity %	Specificity %
Stage 1	26.83	70	79
Stage 2	25.15	71	78.6
Stage 3	23.86	71	57.1

Discussion

Breast cancer is highly heterogeneous in terms of its etiology and pathological characteristics, some cases of breast cancer showing slow development with good prognosis, whereas other cases taking a highly aggressive clinical course [13]. Early-stage detection of this cancer could reduce breast cancer death rates significantly in the long-term. Investigators have studied many breast diagnostic approaches, including mammography, ultrasound, magnetic resonance imaging, positron emission tomography (PET), computerized tomography and biopsy [14]. Biomarker-based methods such as immunohistochemistry, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA) and fluoroimmunoassay also important and provide great information to the diagnostic requirements for breast cancer [15],[16]. Biomarker-based techniques are sensitive and selective, however, they have some limitations such as being expensive, needing trained people, time consuming and complex labelling process are also required [17]. Thus, there is an urgent need to develop a high sensitivity and label-free method for rapidly diagnosing breast cancer [18].

Serum level of CD200 in patients with breast cancer increased with the progression of the disease which can be used as a diagnostic marker to differentiated breast cancer from healthy individual, a study by Giuseppe A. *et.al*, found that CD200 was an excellent marker for the differential diagnosis of chronic lymphocytic leukemia (CD200 positive), and mantle cell lymphoma (CD200 negative)[19]. CD200 is expressed in different neuroendocrine neoplasia, pancreatic islet cells and other normal neuroendocrine cells provides further support for CD200 as a general marker of neuroendocrine differentiation [20]. Serum CD200 level in breast cancer is related with poor prognosis and metastasis as the concentration is positively corelated with the progression of disease, several studies show variation with the prognostic value of CD200 expression, for example, CD200 expression was an independent favorable prognostic factor in patients' with non-small cell lung cancer, on the other hand, it is associated with poor prognosis in hematological malignancies. Lack of CD200 expression in plasma cells has been related to more aggressive multiple myeloma [21]. More recently CD200 odd expression has been proposed as an adverse prognostic factor in AML [22]. A research by Bahrami, A. *et.al*, showed a significant relationship between metastasis status and positive CEA levels, which suggest that high CEA levels decreased sensitivity and specificity for triple-negative breast cancer (TNBC) after received Neoadjuvant Chemoradiation (NCRT) [23]. CD200 was over-expressed and correlated with progression of metastatic melanoma as well as acting as a potential target for therapy [24]. Gorczynski et al. also found a similar results, they discovers that over expression of CD200 level increased breast cancer lymph node metastasis [25]. A study by Jason E. Love, *et.al*, suggests that CD200 is a general sensitive marker for neuroendocrine differentiation, with expression in 87% patient of the Neuroendocrine neoplasms (NENs) in the dataset, including 79 of 83 (95%) gastrointestinal luminal carcinoids, 60 of 72 (83%) pulmonary small cell carcinomas, three of four (75%) pulmonary large cell neuroendocrine carcinomas, 15 of 22 (68%) pulmonary carcinoids, 125 of 146 (86%) Merkel cell carcinomas, and 56 of 60 (93%) pancreatic neuroendocrine tumor [20]. CD200 is highly sensitive in breast cancer patient (88%) sensitive and (100%) specific at (533.18 pg/ml).

Although serum level of CD200R1 is different, stage IV and control showed the lowest level compared to other stages, it cannot be used as diagnostic marker, but it can be used to follow up the patients with confirmed breast cancer as it shows about (70%) sensitivity and different specificities at different concentrations. High expression of CD200R1 in non-small cell lung cancer patients has poor prognosis [26].

Conclusion

The results of this study suggests that serum CD200 concentration can be used as a diagnostic marker to differentiate between healthy individual and breast cancer patients, but it cannot be used as a prognostic marker regardless of increasing in the expression with stage. On the other hand, serum expression of CD200R1 cannot be used as a diagnostic marker to differentiate breast cancer patients from healthy people, but could be used a prognostic marker as the concentration is markedly lowers with progression of the disease specially in stage four patients.

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