Research Article

Serum Tumor Markers and Estrogen hormone are Prognostic Parameters for Clinical Response in Tamoxifen Treated Patients

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ABSTRACT

Breast cancer is the most frequent malignant disease affecting women in the worldwide. Although significant developments have taken place in treatment strategy, tamoxifen remains the standard therapeutic option for breast cancer therapy and for primary prevention of metastatic disease. In breast cancer patients, the most commonly used serum tumor markers are Cancer Antigen 15-3(CA 15-3) and Carcinoembryonic Antigen (CEA), these markers in combination with other parameters like estrogen hormone which is a key factor in the pathogenesis of breast cancer, may have clinical significance in breast cancer surveillance, The study objective was to assess the correlation between therapeutic response and (CEA), (CA15-3) levels and the level of estrogen in tamoxifen treated patients. CA 15-3, CEA and Estrogen levels were assessed among 140 Iraqi breast cancer women who treated with tamoxifen. Breast cancer women that have been recruited in our study were divided into two groups: seventy breast cancer women who had no history of recurrence at the time of sampling and seventy breast cancer women who had recurrence at the time of sampling. tumor marker CA15-3 level and Estrogen level showed lower significant ($p< 0.0001$) level within non-recurrent breast cancer patients than the corresponding level within recurrent breast cancer group, while Tumor marker CEA level was non significantly ($p>0.05$) different in both recurrent and non-recurrent breast cancer patients that have been participated in our study. The present studies suggest that CA 15-3 and estrogen serum levels could act as a prognostic markers for prediction the recurrency of breast cancer. In addition, the cut off values of serum level of both parameters were shown high sensitivity and specificity that may be suggestive of malignant conditions.

Keywords: Breast cancer, CA 15-3, CEA, estrogen hormone.

INTRODUCTION

Breast cancer is the most frequent form of cancer in women worldwide[1]. Steroid hormones (Estrogen and progesterone) have been considered as a key factor in the pathogenesis of breast cancer[2]. Anti-estrogenic drug (Tamoxifen) remains the main hormonal therapy for the treatment of breast cancer women. More than 50% reduction in the mortality is established with 5 years of adjuvant tamoxifen therapy[3]. Although the primary tumor is often treatable, tumor recurrence remains the most common cause of breast cancer mortality[4]. Therefore, it is crucial to identify reliable predictive factors to guide decision making during the treatment of breast cancer in order to improve prognosis. Along with the traditional clinic pathological factors, serum tumor markers have an important role in diagnosis of recurrence, and treatment of several malignancies[5,6] In breast tumor, Cancer Antigen 15–3 (CA15-3) and carcinoembryonic antigen (CEA) are the two most commonly used tumor markers in the clinical settings for more than 30 years[7].

Aim of the study

Study the impact of tamoxifen on the serum levels of tumor marker of breast cancer Ca 15.3, CEA and on the serum level of Estrogen E2 in recurrent and non-recurrent Iraqi breast cancer women recruited from Al Amal hospital in Baghdad.

PATIENTS AND METHODS

Patients

The study was a cross-sectional study carried out at AL-Amal National Hospital in Baghdad, during the period from February, 2017 till the end of September, 2018. The protocol for the study was approved by the Ethical committee of Al-Nahrain Medical College, and informed signed consent was given by each subject after explaining the nature and purpose of study. The study was conducted on one hundred forty women with (ER and/or PR) positive early-stage ductal breast carcinoma. All women included in this study with (aged ranged 45-56) were starting tamoxifen tablet 20mg per oral daily as standard adjuvant therapy. Patients were enrolled after they had completed all primary surgery, radiation, and adjuvant chemotherapy.

They were excluded from the registry if they had started tamoxifen therapy concurrently with either adjuvant chemotherapy or adjuvant radiation therapy (or both) or if they were undergoing other adjuvant endocrine therapies. Other reasons of exclusion using of clonidine, combinations of ergotamine and phenobarbital, or

megestrol acetate for hot flash therapy. Patients who were pregnant or lactating were excluded from the study. Patients who had taken known CYP2D6 inducers or inhibitors within 28 days of the study were also excluded. Patients with a previous history of GI disorders or surgery that may affect the absorption of tamoxifen were excluded from the study. The one-hundred forty recruited women that participated in this study who were on tamoxifen as adjuvant therapy (20mg/day) were divided into two groups:

A - Non-recurrent group: which include seventy breast cancer women who had no history of recurrency even it is locally, regionally or metastasis to a distant area at the time of sampling.

B – Recurrent group: which include seventy breast cancer women who had recurrency either locally, regionally or metastasis to a distant area at the time of sampling

Clinical Data Collection

Clinical data were extracted from the medical records of consenting patients are: date of diagnosis, site (left breast, right breast, or bilateral), type of cancer, histological grade, clinical stage, pathologic stage, number of lymph nodes removed at surgery, number of lymph nodes involved, tumor markers in primary breast cancer tissue (ER, PR, HER-2), date and dose of tamoxifen therapy received, other medications that concurrently used with tamoxifen, date of first recurrence, site of first recurrence, systemic treatment for metastatic disease, date of last follow-up and current status, Ultrasound, bone scan, mammogram, CT- scans, MRI which were done as a routine follow up for each patient.

Sample Collection and Analysis

After approval by the Ethical committee of Al-Nahrain Medical College, blood samples were obtained from eligible patients who had signed informed consent. 5 ml of venous blood were withdrawn from all women participated in this study. the (5ml) was placed in gel tube (EDTA- free tube), serum was aspirated after centrifugation of the blood at 3000 rpm for 10 minutes ; were it utilized for the measurement of E2,CA15.3 and CEA.

Serum analysis

The instrument used for serum determination of Estradiol (E2), Carcinoembryonic Antigen (CEA) and Cancer Antigen (CA 15-3) is Stat Fax 4200-ELISA analyzer Microwell plate Reader (Awareness technology /USA). The Quantitative Determination of CA 15-3, CEA, and E2 Concentration in Human Serum by a Microplate imunoenzymometric assay[8-11].

Statistical analysis

The results were expressed as mean and median ± SD, Un-paired student's t-test and Mann Whitney test were used to examine the difference in the means and medians of the parameters tested in recurrent breast cancer patients compared to non-recurrent breast cancer patients. A p-value of less than 0.01 was considered significant. Chi-sq used to determine the positive and negative readings frequency and percentage of tumor markers.

Receiver operator characteristic (ROC) curve for the estimation of area under the curve reflecting the accuracy and the cut-off values with concurrent sensitivity and specificity of estrogen and tumor marker parameters. $p<0.01$ was considered significant, area >0.7 reflect the accuracy of assessment.

RESULTS

Tumor Marker CA15.3 Level

Majority of the patients of our study, CA15-3 tumor marker level showed lower mean level (18.5U/ml) within non-recurrent breast cancer group than the corresponding level (39.12U/ml) within recurrent breast cancer group, CA15-3 has a lower significant median level (18U/ml) within non- recurrent breast cancer group as compared to its corresponding in recurrent breast cancer group (34.7U/ml) ($p<0.01$) (Mann Whitney test <0.01) (Table 1).

Table 1: Mean and Median of Tumor Marker CA15.3 level in Recurrent versus Non-recurrent groups of Breast Cancer Patients.

	CA15.3 level in recurrent group U/ML N=70	CA15.3 level in non-recurrent group U/ML N=70
Mean	39.12	18.5*
Median	34.7	18*
Standard deviation	14.22	8.09
P value (t-test)	2.0824E-19	
Mann Whitney test	<0.0001	

*: significant difference at $p < 0.01$.

Receiver operator characteristic (ROC) curve for CA15-3

Table 2 and figure 1 showed that the Area Under the Curve for CA15.3 value was highly significant ($p<0.01$) and Excellent assessment (area > 0.7) for reflecting the accuracy.

Concerning the prediction or diagnosis the recurrency, table 3 showed the Cut-off values with concurrent sensitivity and specificity for the value of CA15.3 and the cut-off values that write in bold type showed highly sensitivity and specificity.

Table 2: Area Under the Curve for CA15.3 value

Area Under the Curve				
Area	**Assessment**	**Std. Error**	**P value**	**95% confidence interval**
0.918	Excellent fitness	0.022	1.16827E-17	0.87 – 0.96

Table 3: Cut-off values of CA15.3 for recurrence

Cut-off values for recurrence (greater than or equal to)	Sensitivity	Specificity
3.9	100.00	0.00
5.4	100.00	1.43
11.1	100.00	24.29
11.5	100.00	25.71
11.75	100.00	28.57
12.15	98.57	28.57
14.5	98.57	37.14
15.4	98.57	38.57
16.25	98.57	40.00
16.45	98.57	41.43
16.55	97.14	42.86
17.1	97.14	44.29
20.75	94.29	67.14
21.25	94.29	68.57
22.05	94.29	70.00
22.7	94.29	71.43
24	90.00	74.29
24.35	88.57	77.14
24.7	88.57	78.57
25	88.57	80.00
25.6	88.57	82.86
26.3	88.57	84.29
26.65	88.57	85.71
26.95	85.71	85.71
27.3	85.71	87.14
27.55	84.29	87.14
27.65	82.86	87.14
27.95	81.43	87.14
28.25	81.43	88.57
28.55	80.00	88.57
28.85	78.57	88.57
29	77.14	88.57
29.4	75.71	88.57
29.75	74.29	88.57
29.85	70.00	88.57
33.65	61.43	94.29
33.75	61.43	95.71
33.85	58.57	97.14
34.15	57.14	97.14
34.45	55.71	97.14
34.55	51.43	97.14
34.7	50.00	97.14
34.95	48.57	97.14
60.6	12.86	100.00
75.5	0.00	100.00

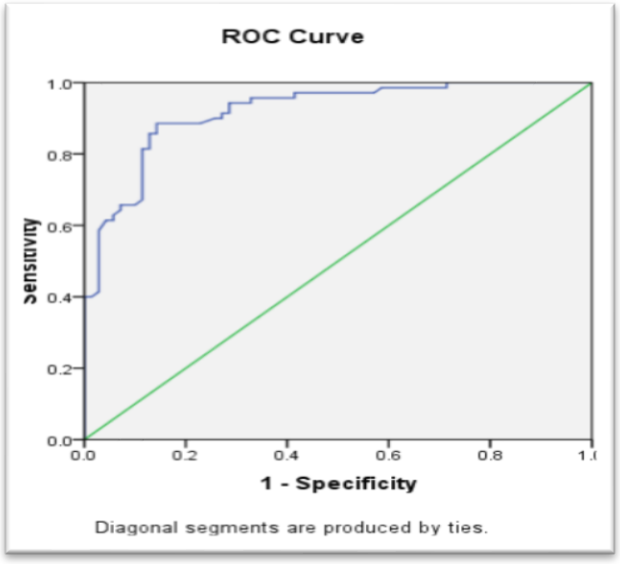

Figure 1: ROC curve of CA15.3 value

Positive/Negative CA15.3 Readings in Recurrent versus Non-recurrent Groups of Breast Cancer Patients

Of the patients of our study, CA 15-3 tumor marker showed 49 positive reading with a percentage of 70% in recurrent group, while in non-recurrent group the positive reading was 8 with a percentage of 11.42%. Furthermore, the negative reading of CA 15-3 tumor marker in recurrent group of breast cancer patients was 21 with a percentage of 30% and 62 in non-recurrent group of breast cancer patients with a percentage of 88.57%. Table 4.

Tumor Marker Carcinoembryonic antigen (CEA) Level

Carcinoembryonic antigen (CEA) level (mean and median) in recurrent group of breast cancer patients were not significantly different compared to the non-recurrent group of current study ($p>0.05$) (Mann Whitney test >0.05). Table 5.

Estrogen (E2) Level

Of the patients of our study, estrogen level showed lower mean level (18.6 pg/ml) within non-recurrent breast cancer group than the corresponding level (30.6 pg/ml) within recurrent breast cancer group, estrogen has a lower significant median level (16.45 pg/ml) within non-recurrent breast cancer group as compared to its corresponding in recurrent breast cancer group (29.55 pg/ml) ($p<0.01$) (Mann Whitney test <0.01). Table 6.

Table 4: The Frequency and Percentage of Positive/Negative CA15.3 Readings in Recurrent versus Non-recurrent Groups of Breast Cancer Patients

CA15.3	Positive	Negative	Total
Recurrent group	49	21	70
%	70	30	100
Non-recurrent group	8	62	70
% Percentage	11.42	88.57	100
Chi-sq, P<0.01			

Table 5: Mean and median of Carcinoembryonic Antigen (CEA) level in Recurrent versus Non-recurrent groups of Breast Cancer Patients.

	CEA level in recurrent group nglml N=70	CEA level in non-recurrent group nglml N=70
Mean	1.85	1.87
Median	1.9	1.8
Standard deviation	0.83	0.63
P value (t-test)	0.82	
Mann Whitney test	0.81	

Table 6: Mean and median of Estrogen (E2) Level in Recurrent versus Non-recurrent groups of Breast Cancer Patients.

	E2 level in recurrent group pg/ml N=70	E2 level in non-recurrent group pg/ml N=70
Mean	30.6	18.6*
Median	29.55	16.45*
Standard deviation	11.58	11.11
P value (t-test)	4.64E-09	
Mann Whitney test	<0.01	

*: significant difference at p < 0.01.

ROC curve for E2

Table 7 and figure 2 showed that the Area Under the Curve for E2 value was significant (p<0.01) and very good assessment (area > 0.7) for reflecting the accuracy. Concerning the prediction or diagnosis the recurrency, table 8 showed the cut-off values with concurrent sensitivity and specificity for the value of E2 and the cut-off values that write in bold type showed highly sensitivity and specificity.

Table 7: Area Under the Curve for E2 Value.

Area Under the Curve				
Area	**Assessment**	**Std. Error**	**P value**	**95% confidence interval**
0.806	Very good	0.038	0.01	0.73 - 0.881

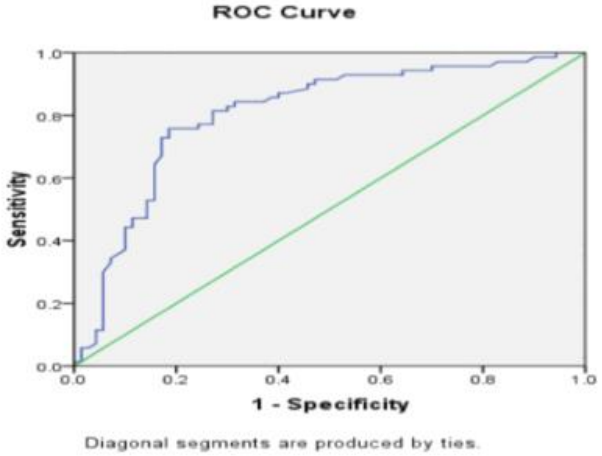

Figure 2: ROC curve of E2 value

DISCUSSION

Breast cancer is a progressive and heterogeneous disease, and one of the most crucial issues in cancer research is the early detection. Because many breast cancers still escape primary detection, identification of tumor markers able to reveal primary stages may significantly reduce associated mortality [12]. Furthermore, an effective follow-up is needed for all treated patients who may develop recurrence of the disease during their life [13]. Possible use of biological markers in breast cancer include diagnosis of the disease early, predicting response or non-response to specific therapies, determining prognosis, observation after primary surgery and monitoring therapy in advanced disease[14]. Nevertheless, prognostic relevance of tumor

markers and clinical usefulness is still controversial especially in patients with early stage disease [15, 16].

Serum tumor markers (STM) are soluble molecules which are released into the blood by cancerous cells or by other cells in response to cancerous cells. STM are the most extensively used in clinical setting as they reflect the dynamic evolution of the disease and their levels can be simply repeated when required [17]. STM are broadly tested for detection of malignancies, for predicting recurrence or assessing clinical outcome and for monitoring the response to antitumor therapies [18, 19].

Of the patients of our study, CA15-3 tumor marker level showed lower mean level within non-recurrent breast cancer group than recurrent breast cancer group, Table 1. As increasing serum levels of CA 15-3 are found during therapy, disease progression may be expected. Contrariwise, declining in the concentrations of the biological tumor marker indicate a positive treatment effect and a regressing or as a minimum stable disease course. This positive correlation between clinical presentation and tumor marker behavior is mentioned by several authors [20, 21].

In agreement with the other literatures, our study shows that metastasizing breast cancers are associated with increased CA15-3 levels, while in non- recurrent breast cancer patients are associated with decreased levels [21, 22]. Accordingly, the main use of this tumor marker may be found in the follow-up investigations of surgically treated breast cancer women [23]. Remarkably, high levels CA 15-3 concentration were found in recurrent breast cancer patients , the CA 15-3 marker concentrations showed a good correlation to the recurrency or metastasis conditions of breast cancer, it has been thought from above results the predictive efficacy of CA 15-3 in metastatic breast cancer as several studies suggest that tumor marker levels correlate with treatment response[24,25].

To evaluate the sensitivity and specificity for the value of tumor marker CA15.3 to predict recurrence of breast cancer, Receiver operator characteristic (ROC) curve have been used for the estimation of area under the curve that reflecting the accuracy and the cut-off values of the serum antigen, (ROC) curve have been showed excellent fitness that serum antigen may be consider as efficient prognostic value to predict recurrency (Area 0.918). Table 2.

Serum concentration of CA 15-3 tumor marker of over 24 U/ML in our study may be suggestive of malignant conditions which have been shown high sensitivity and specificity as shown in table 3 and figure 1.

Of the patients of our study, CA 15-3 tumor marker showed 49 positive reading with a percentage of 70% in recurrent group, while in non-recurrent group the positive reading was 8 with a percentage of 11.42%. Furthermore, the negative reading of CA 15-3 tumor marker in recurrent group of breast cancer patients was 21 with a percentage of 30% and 62 in non-recurrent group of breast cancer patients with a percentage of 88.57%. Table 4.

As a whole, from above results of our finding, CA 15-3 marker concentration showed a good correlation to the breast cancer recurrency. Monitoring CA 15-3 serum concentrations provides a simple way to predict the therapeutic response of patients, hence improving the strategy of therapy and diminishing unnecessary side effects due to unsuccessful treatments.

The currently available finding obtained from our study postulated that there is no correlation between CEA serum concentration with recurrency since CEA level is not significantly different in both of recurrent and non-recurrent breast cancer patients participated in the study. Table 5.

The correlation between the risk of breast cancer and persistently elevated estrogen blood levels has been found consistently in various studies. Studies of breast cancer have been found an increased risk associated with elevated blood levels of endogenous estrogen, these observations support the hypothesis that estrogen is a mammary-gland carcinogen. The mechanisms through which estrogens contribute to each phase of the carcinogenic process (initiation, promotion, and progression) are complex [26, 27]. The evidence recommends the participation of genotoxic metabolites of estrogen and estrogen-receptor–mediated genomic and non-genomic signaling that affect apoptosis and cell proliferation in mammary tissue, the extent to which these pathways contribute to estrogen-mediated carcinogenesis and the mechanisms by which genetic polymorphisms and environmental factors modify the effects of these pathways have need of further exploration[28].

Estrogen level, till now have never been studied the difference in its serum concentration during long term therapy with tamoxifen in both recurrent and non-recurrent perimenopausal breast cancer patients, the present study seems to be the first study that demonstrate the difference in estrogen level in recurrent and non- recurrent breast cancer patients.

Of the patients of our study, estrogen level showed lower mean level within non-recurrent breast cancer group than the corresponding level within recurrent breast cancer group. Table 6.

Additionally, our finding have been determined the sensitivity and specificity for estrogen levels within breast cancer patients participated in the present study to predict recurrence of breast cancer, Receiver operator characteristic (ROC) curve have been used for the estimation of area under the curve that reflecting the accuracy and the cut-off values of the serum estrogen, (ROC) curve have been showed very good fitness that serum estrogen may be consider a good prognostic value to predict recurrency (Area 0.806). Table 7 and figure 2.

Additionally, the sensitivity and the specificity of estrogen for the detection of recurrence in the follow-up of patients with no clinical evidence of disease is related to the cut-off values of estrogen. Serum concentration of estrogen of over 21.15 pg/ml in the study may be suggestive as a prognostic value in recurrent breast cancer which have been shown high sensitivity and specificity as shown in table 8 and figure 2.

Table 8: Cut-off values of E2 for recurrence

Cut-off values for recurrence (greater than or equal to)	Sensitivity	Specificity
1.8	100	0
7.25	98.57143	5.714286
8.05	98.57143	7.142857
8.45	98.57143	8.571429
11.35	95.71429	30
11.85	94.28571	30
14.3	92.85714	42.85714
14.95	92.85714	44.28571
15.4	92.85714	45.71429
19.5	87.14286	60
19.65	85.71429	60
20.75	82.85714	68.57143
21.15	82.85714	**70**
21.45	81.42857	**70**
21.6	81.42857	**71.42857**
21.8	81.42857	**72.85714**
22.1	78.57143	**72.85714**
22.35	77.14286	**72.85714**
22.45	77.14286	**75.71429**
22.65	75.71429	**75.71429**
23.3	75.71429	**77.14286**
23.85	75.71429	**78.57143**
24.35	75.71429	**80**
24.85	75.71429	**81.42857**
25.1	74.28571	81.42857
25.45	72.85714	81.42857
30.4	47.14286	87.14286
30.6	47.14286	88.57143
33	37.14286	90
33.55	35.71429	91.42857
40.05	11.42857	94.28571
42.35	11.42857	95.71429
60.3	2.857143	98.57143
62.65	1.428571	98.57143
67.35	1.428571	100
72.9	0	100

Although various studies suggest that tamoxifen effectively saturate receptors of estrogen during tamoxifen therapy[29]. Proposing that the levels of estrogen may have limited importance during tamoxifen treatment. However, long term exposure to tamoxifen has been shown to induce an adaptive hypersensitivity state in breast tumors to E2[30]. Hence upon development of tamoxifen resistance and hypersensitivity, low concentration of estrogen may stimulate tumor growth [27]; this may explain the observed association between serum estrogen and tumor makers levels as our study have been determined that recurrent breast cancer patients associated with high levels of estrogen and high levels of tumor marker CA 15.3 which may consider as a good prognostic value in determining tamoxifen response therapy. As a consequence, it has been thought in the present study that increase levels of estrogen may be associate with increased levels of tumor marker. However, it has not yet been demonstrated in our study if the use of CEA tumor marker as indicator of recurrence. Besides this, CA 15.3 seems superior to CEA for determination of recurrence in breast cancer of the present study. As a consequence, it has been thought in the present study that using combinations of several markers (e.g. CA 15.3 and CEA), possible to increase the sensitivity of prognostic determination in patients with recurrence. Additionally, it has been postulated in our finding that simultaneous use of tumor marker CA 15.3, estrogen E2 and CEA may allow early diagnosis of metastases and determine the therapeutic response to tamoxifen therapy in patients with breast cancer.

CONCLUSION

Our finding suggest that CA 15-3 and estrogen (E2) serum levels act as a prognostic markers for prediction the recurrency or metastasis of breast cancer. Additionally, the finding of the present study determined the cut off values of serum level of each parameter that have been shown high sensitivity and specificity which may be suggestive of malignant conditions.

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