Exploring The Impact of Capecitabine Treatment on Hormonal and Biochemical Markers in Women with Breast Cancer

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Abstract

Cancer antigen 15-3 (Ca15-3) is a widely used tumor marker, and the serum level of this tumor marker is measured periodically in breast cancer patients during the chemotherapy period by capecitabine, assuming that the higher serum levels of this tumor marker (CA 15-3) can be a potential risk in breast cancer patients. The study aims and examines the serum levels changes of tumor marker (Ca15-3), serum estradiol, and calcium after administration of capecitabine in postmenopausal breast cancer women. The study was conducted on a total of 200 women, including 100 women without breast cancer who served as a control group age ranging (45-75years) and 100 women with breast cancer whose ages ranging from (40-70years). Patients were at the oncology center at Imam al-Hussain medical city in Kerbala, Iraq, were sorted into groups based on their age, and treatment length of capecitabine chemotherapy for this study, which was done between July 2022 and October 2022. The efficacy of capecitabine, the plasma levels of (estradiol, CA 15-3, and calcium) were measured in 100 breast cancer patients who had been taking the drug for at least 3 months. The findings revealed a statistically significant increase (p≤ 0.05) in the concentration of Ca15-3 levels in women with breast cancer compared with the control group, the average levels of estradiol were increased in in postmenopausal breast cancer women and different with normal levels parameters except serum calcium the control group was highly concentration than patients, on the other hand, the average level of serum calcium and estradiol in control groups within the normal range.in conclusion according to the Ca15-3,serum calcium and estradiol levels, The high stability and existence of Ca15-3, serum calcium and estradiol in body serum make them a promising new diagnostic biomarker for breast cancer patients.
Key words: CA 15-3, Breast cancer, capecitabine, Estradiol, Calcium

استكشاف تاثير علاج الكابسيتابين على الموشرات الهرمونية والكيموحيوية لدى النساء المصابات بسرطان الثدي#

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الخلاصة

مستضد السرطان ١٥-٣ (CA15-3) هو علامة ورم مستخدمة على نطاق واسع ، ويتم قياس مستوى المصل لهذا الورم بشكل دوري في مرضى سرطان الثدي خلال فترة العلاج الكيميائي بواسطة كابسيتابين ، بافتراض أن المستويات المصلية الأعلى لعلامة الورم هذه يمكن أن يكون خطرًا محتملاً في مرضى سرطان الثدي ، وتهدف الدراسة وفحص تغيرات مستويات المصل في علامة الورم Ca15.3 ، واستراديول المصل ، والكالسيوم بعد تناول الكابسيتابين في النساء بعد سن اليأس. أجريت الدراسة على ما مجموعه ٢٠٠ امرأة ، ١٠٠ امرأة غير مصابة بسرطان الثدي والذين خدموا كمجموعة اصحاء تتراوح أعمارهم بين (٤٥-٧٥ سنة) و ١٠٠ امرأة مصابة بسرطان الثدي تراوحت أعمارهن بين (٤٠-٧٠ سنة). تم اخذ عينات الدم من المرضى مركز الأورام في مدينة الإمام الحسين الطبية في كربلاء بالعراق إلى مجموعات بناءً على أعمارهم ومؤشر كتلة الجسم ومدة المرض وطول العلاج لهذه الدراسة ، والتي أجريت بين يوليو ٢٠٢٢ وأكتوبر ٢٠٢٢ ، تم قياس فعالية الكابسيتابين ومستويات البلازما من (استراديول ، مستضد السرطان ١٥-٣ ، والكالسيوم) في ١٠٠ مريض بسرطان الثدي ممن تناولوا الدواء لمدة ٣ أشهر على الأقل. كشفت النتائج عن زيادة ذات دلالة إحصائية (P< 0.05) في تركيز مستويات مستضد السرطان بعلامة الورم ١٥-٣ عند النساء المصابات بسرطان الثدي مقارنة مع مجموعة السيطرة ، وسرطان الثدي (BC) هو أكثر أنواع السرطان انتشارًا ، ومتوسط مستويات المصل. تمت زيادة الإستراديول لدى

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المريضات اللاتي يعانين من العلاج الكيميائي لسرطان الثدي ويختلفان مع المعدل الطبيعي ماعدا الكالسيوم فقد اظهر تركيز عالي في الاصحاء مقارنة مع المرضى، كما بين متوسط مستوى الكالسيوم في الدم والإستراديول في مجموعة التحكم ضمن المعدل الطبيعي ، في الخلاصة وفقًا لـ مستويات المستضد السرطان ١٥-٣ ، ومستويات الكالسيوم والإستراديول في الدم ، ثبتت بانها علامة بيولوجية تشخيصية جديدة واعدة لمرضى سرطان الثدي.

الكلمات الافتتاحية: مستضد السرطان ١٥-٣ ، سرطان الثدي ، كابسيتابين ، استراديول ، كالسيوم

Introduction

Breast cancer is the most common cause of cancer death for women worldwide and the fifth type of cancer leading to death globally, despite the development of detection and treatment methods, there are an increase in the incidence and mortality of the disease in middle and poor countries. The breast cancer accounts about 30% (or 1 in 3) of all new female cancers each year [1]. It is the most common cancer among women in developed countries, accounting for 23% of all cancers [2], and In adult females, breast cancer was the most common representing 45.42% of cancers, followed by lymphoma (6.13%), ovarian cancer (5.12%) [3]. In men, breast cancer can also be present, although it only represents 1% of all diagnosed breast cancers.

Breast cancer is a complex disease caused by common changes in the population in a number of genes, in combination with environmental factors, the identification and characterization of these common changes have been studies many years ago. These are case-control association studies designed with a selection of 33 candidate genes, 19 of them involved in DNA repair functions, and 14 genes with functions in the cell cycle control, genotyping a total of 169 Single nucleotide polymorphism (SNPs) in 547 cases of breast cancer [4]. Capecitabine belong to antineoplastics (cancer medicines), It interferes with the growth of cancer cells, which are eventually destroyed by the body, it is an antimetabolic fluoropyrimidine deoxynucleoside carbamate and is administered orally [5].

Capecitabine peak concentrations were measured at the first observation after drug administration. Nevertheless, the median Cmax levels for capecitabine and metabolites were slightly underpredicted. A three-compartmental distribution model for capecitabine was considered to improve the estimation of median Cmax levels [6].

Capecitabine contain active metabolites, they may be affected by dihydropyrimidine dehydrogenase (DPD) insufficiency, the DPD insufficiency is a genetic disregulation that is caused by mutations in the DPD gene. These mutations result in greatly decreased or absent activity of the enzyme that is responsible for metabolizing these compounds fluorouracil [5-FU] [7]. This enzyme changes the structure of uracil so that it becomes another molecule known as 5,6-dihydrouracil. It also changes the structure of thymine so that it becomes 5,6-dihydrothymine. The body either eliminates the molecules that are produced as a byproduct of the breakdown of pyrimidines or uses them in other cellular processes [5]. Aim of study: this study was to determine the association between CA15-3 and Calcium and estradiol levels in breast cancer women and to evaluate the relationships between these factors and clinicopathological factors in postmenopause with breast cancer.

Subjects, Materials and Methods

Patients and control

A total of 200 women participated in the study; as a control group, 100 of the participants did not have breast cancer, while the remaining 100 were diagnosed with the disease, the diagnosis of breast cancer was dependent on the American Cancer Society screening guidelines [6]. All control were free from any chronic disease or auto-immunodisease The research was carried out between July 2022 and October 2022 in the laboratories of the College of Pharmacy at the University of Kerbela as well as in the Imam AL-Hussein Medical City and Oncology Center in Kerbala. The protocol of the study was given the go-ahead by the ethical committee of the College of Pharmacy at the University of Kerbela, and a signed informed consent form was provided to each subject after the nature and purpose of the study were explained to them; inclusion criteria was include personal history of breast cancer, chest radiation and Pulling in of the nipple or pain in the nipple area and women taken capacetabine chemotherapy otherwise exclusion criteria women less than 50 years old, no thickening or no swelling of part of the breast, women taken other chemotherapy.

CA 15-3, Estradiol and Ca^{2+} Concentration

Five milliliters of blood was drawn by vein puncture from all individuals participated in this study. The serum was obtained by allowing the samples to coagulate at room temperature and then centrifuging them for 15 minutes at a speed of 2000 revolutions per minute. The serum was then frozen at -20 degrees Celsius until it was needed.

The quantitative measurement of CA 15-3 levels in human serum was carried out with the Enzyme Linked Fluorescent Assay technique (ELFA), which was based on the quantitative sandwich principle and performed in accordance with the manufacturer's instructions (Biomerieux/France)[7].

The quantitative determination of concentration of estradiol level in human serum by Chemiluminescent Immunoassy (CLIA) [8], which is

a competitive binding immunoenzymatic assay, Cobas 6000 analyzer series was used for the measurement of total calcium levels in patient's sera [9].

Statistical analysis

The statistical analysis consisted of the T-test, which was conducted with the Statistical Package for the Social Sciences (SPSS version 25.0) software, was used to compare the means of the variables that were collected from patients and those collected from the control group. The normal data were shown as the mean value plus the standard deviation (SD). If the P value was less than 0.05, this indicated statistical significance.

Results and Discussion

Information on the population's demographics

The studied population included 100 female patients with breast cancer. Participants' average age at study were 55.36 ± 10.85 years (range: 45-65). Eighty six percent were married and only (14%) single. There was a 62% disparity between the women who had a family history of breast cancer and those who didn't (38%) among those who were diagnosed. Cancer patients who had the disease on their left sides recorded as 33%, while those on their right sides was recorded as 67%. It is also recorded that 90% of patients have already had surgery, 88% of patients already have radiation therapy, and 92% of patients have had chemotherapy Figure (1).

As indicated in table 1, the average levels of serum calcium was lower than control, it was recorded as (9.34 ± 3.5) mg/dl, whereas the estradiol were increased in patient had breast cancer chemotherapy compared with controls group, hich ranged as (10-66 pg/ml) , however the average level of both: serum calcium and estradiol in control and patients groups are within the normal reference levels.

The findings demonstrated a statistically significant rise in the amount of CA 15-3 found in breast cancer patients $(136.4\pm36.7$ U/ml) in comparison to the level found in the control group $(31.68\pm11.32$ U/ml ; P= 0.034).The group under study consisted of one hundred different breast cancer patients who were female, the average age of the participants was 55.36 ± 10.85 years (range: 45-65), and control groups average age (53.78 ± 11.56) [10]. The results showed that a higher incidence of breast cancer on the right side (67%) compared to the left side (33%), this result was in agreement with Han et al., [11] who was found 81 women were found to have original breast cancer for both breasts, with 35 cases being found in the left breast first and 46 cases being found in the right breast first.

The findings of the current study are in agreement with the findings of the previous study [12], which indicated an increase in the level of CA 15-3 in breast cancer women who had metastatic disease. Additionally, in the histological study, a high level of microRNAs have an effect on a wide variety of oncogenes and suppressor genes, all of which play a role in the development, progression, and spread of cancer [13]. These findings are consistent with the findings of the present study which also found an increase in the level of CA 15-3 in breast cancer patient, the use of CA15-3 as a biomarker is restricted despite the fact that it is easily accessible in the serum. It is used as a screening tool for various cancers, including pancreatic, lung, ovarian, colon, and liver cancers, and it can be elevated in benign liver and breast cancer [14].

Regarding to the level of estradiol (E2) in the serum, the present study showed that significant differences (p<0.05) between the studied patient with control groups, Estrogen receptor (ER) is one of nuclear receptor family which has been activated by 17-β-estradiol and there are two isoform of ER i.e. ERα and ERβ that encoded by genes located in different chromosome [15,16]. About 65% of breast cancer women less than 50 years old and 75% of older women with breast cancer are estrogen receptor positive [17].

Estrogen is essential for the normal growth and growth of breast tissue and it also considered a major risk factor for breast cancer when exposed to high level of estrogen [18], Estrogen signals through its two receptors (ERα and ERβ),but only ERα is essential for the development of breast and activates proliferative signaling in the normal and breast cancer ,whereas ERβ generally antagonize ERα in the breast [19].

According to duration of treatment the levels of serum biomarkers were also investigated dependent on the length of time that patients were treated with capecitabine. In general, patients with breast cancer were shown to have a decreasing range of Calcium levels when comparing those whose treatment duration was less than 5 years to those whose treatment duration was more than 5 years. Although hypercalcaemia is a frequent complication of breast cancer which causes significant morbidity and mortality. Most commonly, it occurs in patients with multiple skeletal metastases. [19]. Elevated level of calcium in the bloodstream is most often a complication of cancer and is referred to as hypercalcaemia of malignancy ,which may be a life-threatening emergency [20].Up to 30% of all people with cancer will develop a high calcium level . However, they are many types of cancers that are most commonly associated with high blood calcium when they are first diagnosed. breast cancer. [21, 22].

The chance of developing breast cancer grows in tandem with endogenous estrogen levels, according to prospective research. Tamoxifen and raloxifene, two selective estrogen receptor modulators, inhibit the actions of endogenous estrogen in the breast, hence lowering the risk of breast cancer. It follows that endogenous estrogen

levels may moderate the effects of selective estrogen receptor modulators [23].

The risk of breast cancer and the effect of it depend on estradiol concentrations of estradiol. Specifically, hypothesized that women with undetectable serum concentrations of estradiol would have a very low breast cancer risk that would not be further reduced [24].

About 80% of all breast cancers are "Estrogene-positive." That means the cancer cells grow in response to the hormone estrogen. About 65% of these are also "Progestrone-positive." They grow in response to progesterone hormone [25].

In conclusion: serum levels of tumor marker (CA15.3), and estradiol are potentially useful novel diagnostic biomarker for

postmenopausal women with breast cancer due to their high levels; and may give a clear idea about prognosis of sever condition; this may improve the overall clinical outcome.

Table 1. Comparison of Tumor marker (CA15-3), Estradiol and Calcium.

Variables	Patients	Control	P value
CA 15-3 U/ml	136.4±36.7	31.68±11.32	0.01
E2 pg/ml	89.55± 14.7	22.37± 9.67	0.01
Ca mg/dl	9.34±3.5	10.02±6.1	0.01
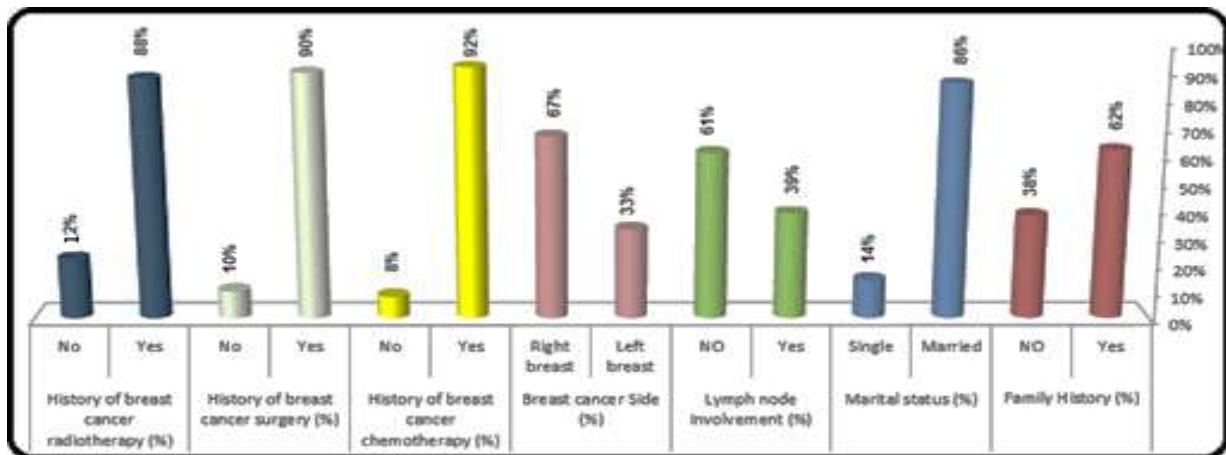
Figure 1. Demographic data for all patient suffering from breast cancer

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Ethics Statements

The study received ethical approval from the Ethical Committee of the Faculty of Pharmacy, University of Kerbala , Iraq .(No. 2022HU3).

Conflict of Interest

All obstacles were overcome by the researchers through personal efforts.

Author Contributions

Everything mentioned in the research is the result of the researchers' efforts, and the tasks were distributed according to the availability of capabilities and time

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