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Genetic Polymorphic Impact of Metabolizing Enzyme (CYP3A4 and UGT1A4 genes) on Anastrazole Response in Iraqi Breast Cancer Women

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1. Abstract

1.1. Background and Objective: Anastrazole is an aromatase inhibitor used widely in therapy of breast cancer and has been metabolized by CYP3A4 and UGT1A4 in liver. Breast cancer is the most common cancer type in worldwide and the second causes of death after lung cancer and the one of therapy that use in its treatment is aromatase inhibiter, anastrazole has been indicated CYP3A1 and UGT1A4 are the main metabolizing enzyme, so the interindividual variation in anastrazole response are due to polymorphism of these gene. We have aimed to determine whether CYP3A4*22 and UGT1A4*2 single nucleotide polymorphisms can have affected on the response of anastrazole.

1.2. Method: 100 Iraqi females with hormone positive breast cancer were included in this study. patients were genotyped for SNPs in the CYP3A1 and UGT1A4 genes to research for response to anastrazole thought measured serum level of estradiol (E2) and tumor marker CA15.3. Highly polymorphic CYP3A4*22 (rs35599367) and UGT1A4*2 (rs6755571) were detected with different genotypes in variable percentage in Iraqi breast cancer women.

1.3. Results: For rs35599367 found that the wild genotype(GG) and for rs6755571 the mutant genotype (TT) were most abounded in 100 breast cancer women and also (AA) another mutant genotype of rs6755571 detected but in low percent. Non –significant association between different detected genotype of both SNPs and serum estradiol level, elevation of serum CA15.3 level and development of arthralgia.

1.4. Conclusion: Both SNPs suggesting had no effect on the serum levels of E2 and CA15.3 and development of arthralgia.

2. Introduction

Breast cancer is the most common type of cancer among women other than nonmelanoma skin cancer representing approximately 30% of all new cancer cases in females, and the second causes of death after lung cancer, that accounting for an estimated 15% of all cancer –related death in women [1], and reported about 20-30%of breast cancer females may develop metastasis after diagnosis and primary treatment and about 90% of cancer –related deaths are attributed to metastasis [2]. The overall survival rate of breast cancer patient without metastasis for 5-years is more than 80% while metastasis can lead to reduction this rate to approximately 25% [3] Breast cancer is a histologic diagnosis made according to standardized pathologic criteria. The invasive ductal carcinoma (50%-75%) is the most common histological breast cancer, followed by invasive lobular carcinoma (5%-15%) [4]. Estrogen receptor alpha (ERα) that expressed in approximately 70% of invasive breast cancer and epidermal growth factor 2 (HER2) which overexpressed in about 20% of breast cancer are the main molecular targets in breast cancer [5]. The main goals of treatment of nonmetastatic breast cancer are eradication of tumor from breast and regional lymph nodes and preventing recurrence or metastasis while for metastatic breast cancer the goals are prolonging life and symptom palliation [6]. The treatment of breast cancer includes local therapy that consist of mastectomy or lumpectomy and systemic therapy that may

be neoadjuvant (preoperative), adjuvant (postoperative) or both [7]. Anastrazole is an aromatase inhibitor that inhibited the conversion of androgens to estrogen so decrease circulating estrogen level that as systemic therapy to treat pre- and postmenopausal women with breast cancer that give as once daily dose (1mg) for 5-years [8]. Anastrazole undergo hydroxylation, N-dealkalytion and glucuronidation through CYP3A1 and UGT1A4 in liver to produce inactive metabolite so the metabolism-related polymorphisms play important role in the interindividual variation [9]. So the polymorphisms of CYP3A4 and UGT1A4 can effect on concentration and response of anastrazole and its metabolites according to type of SNPs [10], CYP3A4*22(rs35599367) and UGT1A4*2(rs6755571) were found in studies decrease enzymatic activity in patients with cancer [11, 12]. Cancer antigen (CA15-3) is one of tumor markers that found in serum, its level elevated in early stage of breast cancer but because of lack of organ and tumor specificity it's not specific biomarker for breast cancer and usually used for therapy monitoring [13].

3. Materials and Methods

3.1. Study Sample

The study is cross-sectional observational study that include Iraqi female patient with hormone positive breast cancer treated with (1 mg) once daily anastrazole (arimidex) at the imam Hussein city of medical/oncology center in kerbala, during the period from (sep.2019 – dec.2020). The study's protocol was approved by the ethical committee of pharmacy college/ kerbala university, after explain the details about the nature and aim of study, each patient was given an informed signed consent form. The study was conducted on 100 females with range of age (34-76) with hormone receptors (ER and/or PR) positive breast cancer. women included in this study were ER and/or PR positive breast cancer and taking daily anastrazole tablet (1mg) at least six months after starting the treatment. Women were taking other adjuvant endocrine therapies, those that start anastrazole therapy along with either adjuvant radiation or adjuvant chemotherapy or both, and also females who taken drugs that induce or inhibit CYP3A4/UGT1A4 and who have a past history of GI surgery or disorder all of them were excluded from study. Pregnant and lactating patient were ignored too.

3.2. Clinical Data Collection

Some clinical information was taken from the patient themselves such as age, weight, height, academic achievement, workplace, marital status, family history, pre-and postmenopausal and breast feeding, another information from medical record of these women which include date of diagnosis, site and type of breast cancer, stage and grade, dose, duration and time of anastrazole

3.3. Sample Collection and Analysis

(5ml) peripheral blood sample was obtained from breast cancer patient which divided into 2ml put in EDTA tube for genetic analysis and 3ml place in gel tube which put in centrifuge at 3000 r/m for 10 minutes to separate serum; were it use for the measurement of CA15.3 and E2.

3.3.1. Genotyping Analysis

Genetic variants were genotyping into two genes involved in metabolism of anastrazole CYP3A4 and UGT1A4, one SNP for each gene (rs35599367 and rs6755571) respectively

3.3.1.1. DNA Extraction: Genomic DNA was isolated from peripheral blood sample using a commercially available kit (G-DEX-TM IIb for blood genomic DNA extraction kit, Intron, Korea) according to manufacturer's protocol

3.3.1.2. PCR Analysis: SNP of CYP3A4 (rs35599367) gene was identified by ARMS-PCR and SNP of UGT1A4(rs6755571) was identified by ASP-PCR with specific primers and thermocycler program for each SNP as show in tables 1-4.

Table 1: SNPs of CYP3A4 with their primer sequences and their product size.

SNPs	Primer sequence	Product size
O-F	5 ' AGGGGTCTTGTGGATTGTTGA 3 '	474
O-R	5 ' CACCTGTCTTGAGCCCCTTAG 3 '	
I-F allele G	5 ' GATGCAGCTGGCCCTACG 3 '	215
I-R allele A	5 ' AGTGTCTCCATCACACCCAGT 3 '	297

Table 2: PCR thermocycler program for CYP3A4 gene

Steps	Temperature (°C)	Minute: second	Cycles
Initial denaturation	95	03:00	
Denaturation	95	00:30	35
Annealing	60	00:30	
Extension	72	00:55	
Final extension	72	5:00	

Table 3: SNPs of UGT1A4 with their primer sequence and their product size.

SNPs	Primer sequence	Product size
F-C	5 ' CTCCTCCTCAGTGTCCAGC 3 '	242
F-A	5 ' GCTCCTCCTCAGTGTCCAGA 3 '	243
F-T	5 ' GCTCCTCCTCAGTGTCCAGT 3 '	243
Reverse primer	5 ' TGAGTGTAGCCCAGCGTAAC 3 '	

Table 4: PCR thermocycler program for UGT1A4 gene.

Steps	Temperature (°C)	Minute: second	Cycles
Initial denaturation	95	03:00	
Denaturation	95	00:30	35
Annealing	60	00:30	
Extension	72	00:55	
Final extension	72	5:00	
Hold	95	03:00	

3.3.2. Biochemical analysis

3.3.2.1. CA15.3 level: The serum CA15.3 level was determining by using Minividas (Biomerieux/France) instrument that depend on Enzyme Linked Fluorescent Assay (ELFA) technique, the kite used in procedure was already done. Normal value of CA15.3 was (5u/ml)

Procedure

- At the beginning, the required reagents should be placed out of refrigerator and left at room temperature for about 30 minutes.
- The calibrator, control and sample were mixed by using vortex
- The "153" SPRs and "153" strips were inserted into the apparatus.
- The assay was started as directed in the user's manual. All the stages were done automatically by the instrument.
- The analyze was completed through 60 minutes.

3.3.2.2. Estradiol (E2) level: The serum estradiol level was determined by using CL-series Chemiluminescence Immunoassay (CLIA) analyzer (Mindray/China) which is a competitive binding immunoenzymatic assay. The kit used in assay was already made. estradiol normal values were (follicular phase 20-138 pg/ml, ovulation phase 100-400pg/ml, luteal phase 31-317pg/ml and postmenopausal <25-84pg/ml)

Procedure

The first step, gently inverted the unopened E2 reagent at least for 30 times in order to resuspend the micoparticle which have precipitated during storage, then the E2(CLIA) reagent kit was loaded on the instrument. only35 µl of sample need in this assay.

3.3.3. Statistical Analysis

Result of this study analyzed statistically through Statistical Package for Social Science (SPSS) version 15 USA for windows software. The genotyping results expressed as percentage and biochemical results normally distributed and have been shown as mean ± SD. ANOVA: single factor was used to compared the biochemical parameters among detected genotypes, A P-value less than 0.05 was considered significant. A Chi esquire test was to establish any significant differences among categorical results. To show the association of detected genotypes with elevation of serum CA 15.3 level and with development of arthralgia used Odds ratio (P-value less than 0.05 was considered significant).

4. Results

4.1. Subject's demographic data

The age of patients involved in this study at time of sampling 53.14 (34-76), (94%) married women and (6%) unmarried, (5%) premenopausal while (95%) postmenopausal, (64%) breast feeding women and (36%) non and mix breast feeding, (12%) of women with family history of breast cancer corresponding to (88%) had no family history, (49%,48%,3%) of patients had cancer in left, right and in both breast respectively, (6%) of patients with PR or ER positive while (94%) with PR and ER positive breast cancer, (89%) of studied women had suffered from arthralgia while (11%) had not table 5.

Table 5: Demographic data of breast cancer patients

Parameters		%Patients
Age (mean ,range)		57.4 (34-76)
Marital status	Married	94%
	Unmarried	6%
Menopausal state	Premenopausal	5%
	Postmenopausal	95%
Breast feeding	Yes	64%
	No	19%
	Mix	17%
Family history	Yes	12%
	No	88%
Breast cancer site	Left	49%
	Right	48%
	Lift and right	3%
	Positive PR and ER	94%
	Positive PR or ER	6%
Arthralgia	Yes	89%
	No	11%

4.2. Genetic Analysis

4.2.1. The detected genotypes of rs 35599367 in the Iraqi breast cancer females

For rs35599367, the wild genotype (GG) was observed as the most frequent genotype in 100 Iraqi women with breast cancer (38%) while (37%) of patients detected with mutant genotype (AA) and (25%) with heterozygous genotype (GA). And for rs6755571 the mutant genotype (TT) was founded in (36%) of breast cancer females that involved in this study, only (4%) of patients detected with (AA) which also mutant genotype and (8%) for wiled genotype (CC), heterozygous genotypes also detected in different frequencies CA (17%), TA (6%), CT (29%), As in table 6.

Table 6: The distribution of detected genotypes of rs35599367 and rs6755571 in the Iraqi breast cancer females.

SNP	Genotypes	Percentage
rs35599367 G>A	GG	38%
	AA	37%
	GA	25%
	Total	100%
rs6755571 C>A,T	AA	4%
	CA	17%
	CC	8%
	CT	29%
	TA	6%
	TT	36%
	Total	100%

4.3. Biochemical Analysis

4.3.1. Serum Estradiol Level (E2)

4.3.1.1. Serum level of estradiol among detected genotypes of rs35599367 in Iraqi breast cancer females

(Table 7) show that the highest serum level of estrogen (21.07 pg/ml±12.9) had been observed in patients with (AA) mutant genotype while the lowest serum estrogen level (9.69pg/ml± 9.63) had been founded in patients harboring heterozygous genotype (GA), similarly patients with wild genotype (GG) had low level of estrogen in serum (19.63 pg/ml ± 10.5), that show non-significant differences between different genotypes of rs35599367 that detected in this study. While for rs6755571, Highest serum estradiol level of patients harboring (AA and TT) mutant genotypes (26.51 pg/ml±10.32) and (21.29 pg/ml±9.68) respectively corresponding with lowest serum estradiol level of patients holding wild genotype (CC) (17.06pg/ml±9.65), also low serum level of estradiol observed in breast cancer women with heterozygous genotypes (CA, CT, TA).

Table 7: Serum level of estradiol among detected genotypes of rs35599367 and rs6755571 in Iraqi breast cancer females

SNP	Genotypes	Mean (E2)pg/ml ±SD	P-value
rs35599367 G>A	AA	21.07 ± 12.9 a	0.83 N.S
	GA	19.69 ± 9.63 a	
	GG	19.63 ± 10.5 a	
rs6755571 C>A,T	AA	26.51 ±10.32 a	0.77 N.S.
	CA	19.45 ±16.96 a	
	CC	17.06 ±9.652 a	
	CT	19.19 ± 9.84 a	
	TT	21.29 ± 9.68 a	
	TA	20.24 ± 9.69 a	

P value derived from ANOVA test, Significant<0.05, non-significant: p>0.05, values expressed as mean±standared deviation (SD), same litters mean no significant differences.

4.3.2 Serum Tumor Marker (CA15.3) Level

4.3.2.1 Above or within normal level of serum CA15.3 among different detected genotypes of rs35599367 and rs6755571 in Iraqi breast cancer females.

In the current study, normal serum CA15.3 level founded in 89 patients with breast cancer and only 11 patients had elevated level of serum CA15.3. (35) of women with (AA) genotype, (23) of women with (GA) genotype and (31) of breast cancer women with (GG) genotype detected with serum level of CA15.3 within normal limit and (2) of breast cancer women with (AA and GA) genotype and (7) of women with (GG) genotype had serum CA15.3 level above the normal value. And for rs675557 normal serum CA15.3 level founded in 89 patients with breast cancer and only 11 patients had elevated level of serum CA15.3. the number of women with normal serum level of CA15.3 as follow: (1) for (AA), (15) for CA, (7) for CC, (33) for CT, (6) for TA and (27) for TT. While (3) of breast cancer women with (AA and CT) genotype and (2) of women with (TT), only (1) of breast cancer patients with (CC) genotype and no patient with (TA) detected with serum CA15.3 level above the normal value.

4.3.2.3 The odds ratio of the different detected genotypes of rs35599367 and rs6755571 in elevation level of serum CA15.3 in Iraqi breast cancer females

Both SNPs had non-significant effect in elevation serum level of

CA15.3 in patients involved in this study in term of odd ratio (odd ratio 0.34.p>0.05) for rs35599367 and (odd ratio 1.29, p>0.05) for rs 6755571.

4.4 Arthralgia

4.4.1. Association the different genotypes of Rs35599367 and Rs6755571 in the development of arthralgia in Iraqi breast cancer females

In term of odds ratio both SNPs rs35599567 (CI-95% (1.03) odds ratio (0.28-3.78) and rs6755571 (CI-95% (1.15) odds ratio (0.32-4.35) had non-significant association with development of arthralgia in breast cancer patients that involved in this study.

5. Dissection

Third generation aromatase inhibitor(anastrazole) consider as one of choice drug that use as adjuvant therapy for pre- and postmenopausal ER and/or PR breast cancer and also for advanced-stage disease [14]. polymorphism of anastrazole metabolizing enzymes (CYP3A4 and UGT1A4) may play a role in the interindividual variability in the response and adverse effect of anastrazole and breast cancer clinical outcome [15] many studies observed that Rs35599367 which is intronic variant reduce the CYP3A4 mRNA in liver expression and activity [16]. In the current study, (table 7) show that the wild genotype (GG) of Rs35599367 detected as the most frequent genotype (0.38) compared with mutant (AA, 0.37) and heterozygous (GA,0.25) genotype while mutant genotype detected in others studies with very low frequency for example in Gordian patients (0.02) and (0.05-0.07) in Caucasian while Asian and African below (0.01) [16-19].

For RS6755571 , (0.36) of females included in this study holding mutant genotype (TT) , (0.04) holding (AA) also mutant genotype and (CC) wild genotype founded in (0.08) of 100 breast cancer females and this incompatible with distributions of this genotypes in Croatian populations that have wild type in high percent (96%) and low percent of (CA) genotype while no detected of mutant genotype in the same papulation and in Malays and Chinese while in Caucasian and Indian was (0.08 and less than0.01) the percentage of (AA) respectively as in table 8 [10, 20].

Estradiol is one of end products of androgens conversion to estrogens by aromatase and can be use as indication for anastrazole response because anastrazole inhabit aromatase so reduce estradiol level [21] anastrazole convert to inactive metabolite through hepatic CYP3A4 and UGT1A4 [22], different studies with different drugs such tamoxifen ,exemestane and lamotrigine showed the patients holding either CYP3A4 (Rs35599367) or UGT1A4(Rs6755571) have low activity of anastrazole metabolizing enzyme and considered as poor metabolizer [12, 18, 19], so according to these data the patients holding either (AA) of Rs35599367 or (AA,TT) of (Rs6755571) have low estradiol level but the result of this showed non-significant association (p>0.05) between both SNPs and estradiol level women holding mutant genotype have high serum estradiol level.

89 patients had serum CA15.3 level within normal values and 11 patients had elevation level of serum CA15.3 and non-significant differences in the level of CA15.3 among detected genotype of Rs35599367 and Rs6755571, so this may have indicated that these SNPs and CA15.3 level were independent variables and SNPs may have had low or no impact on level of serum CA15.3 and may no effect on response of anastrazole.

Similarly, in term of Odds ratio there was non-significant association between polymorphism of CYP3A4 and UGT1A4 gene and elevation level of serum tumor marker (CA15.3).

Arthralgia is the main side effect of anastrazole that effect the life quality of women and may lead to early therapy discontinuation [23].

In this cross-sectional observational study observed that non-significant association between development of arthralgia and genotypes of Rs35599367 and Rs6755561 detected in patients involved in this study (in term of Odds ratio), but observed more than half of studied breast cancer patients treated with anastrazole had developed arthralgia symptoms, this may be due to polymorphic effect of other genes that responsible for estrogen synthesis such as aromatase gene (CYP19A1) [24,25].

Table 8: The distribution of above or within normal limit of CA15.3 in different detected genotypes of rs35599367 and rs6755571in Iraqi breast cancer females.

SNP	Genotypes	Serum CA15.3 level within normal limit (n)	Serum CA15.3 level above normal limit (n)	
rs35599367 G>A	AA	35	2	
	GA	23	2	
	GG	31	7	
Total		89	11	
rs6755571 C>A,T	AA	3	1	
	CA	2	15	
	CC	1	7	X^2= 3.55
	CT	3	33	Df=2
	TA	0	6	P>0.05
	TT	2	27	
Total		89	11	

X2= chi-sq., non-significant: p>0.05., DF= degree of freedom, n: number of patient.

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