EFFECT OF ERB2 ILE655VAL POLYMORPHISM ON TRASTUZUMAB-INDUCED CARDIOTOXICITY IN WOMEN WITH HER2-POSITIVE BREAST CANCER (PKP-005)

C. Gómez Peña[1], C. García Fernández[1], C.L. Dávila Fajardo[1], J.G. Sánchez Ramos[1], S. Ruiz Fuentes[1], J.J. Fernandez Ávila[2], M.R. Cantudo Cuenca[3], I. Blancas López–Barajas[1], R. Damas Fuentes[4], J. Cabeza Barrera[1]
[1]Hospital San Cecilio, Granada, Spain. [2]Complejo hospitalario Torrecardenas, Almería, Spain.
[3]Hospital Virgen de Valme, Sevilla, Spain. [4]Hospital Doctor Negrín, Las Palmas de Gran Canaria, Spain.

JUNTA DE ANDALUCIA
Servicio Andaluz de Salud
CONSEJERIA DE IGUALDAD, SALUD Y POLITICAS SOCIALES

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DE FARMACIA DE GRANADA

BACKGROUND

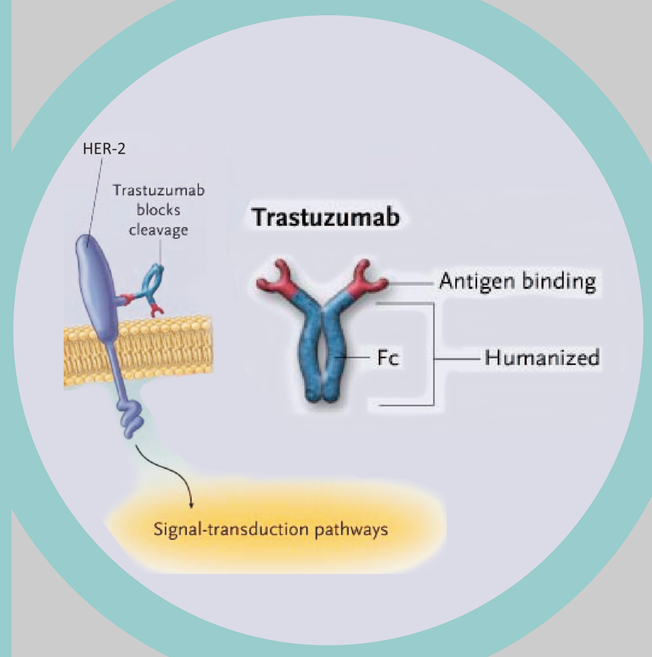
HER2 (ERB2, neu) is a proto-oncogene which encodes a trasmembrane protein with tyrosine kinase activity. Trastuzumab (Herceptin®), a humanized monoclonal antibody which binds to the HER2 extracellular domain, is used for HER2 positive breast cancer's treatment. Although it is well tolerated, it has a significant adverse effect: cardiotoxicity.

PURPOSE

To evaluate the possible effect of ERB2 gene polymorphism at codon 655 (ATC/Isoleucine to GTC/Valine) (rs1136201) in cardiac disfunction related to trastuzumab in women diagnosed with HER2 positive breast cancer.

Parameter	N (%)
Diagnosis age of patients (media, SD)	51.11 (12.16)
Menopausal status	
Pre	28 (51.9%)
Post	26 (48.1%)
Stage	
I	20 (37.04 %)
IIa	9 (16.67 %)
IIb	6 (11.11 %)
IIIa	7 (12.96 %)
IIIb	2 (3.70 %)
IV	10 (18.52 %)
Histological grade	
1	4 (7.41 %)
2	22 (40.74 %)
3	19 (35.19 %)
Estrogen receptor status	
Positive	34 (62.96 %)
Negative	20 (37.04 %)
Progesterone receptor status	
Positive	30 (55.6%)
Negative	24 (44.4%)
Axillary lymph node	
Yes	23 (42.6%)
No	31 (57.4%)
Antraciclines neoadyuvance	
Yes	19 (35.2%)
No	35 (64.8%)
Antraciclines adyuvance	
Yes	26 (48.1%)
No	28 (51.9%)
Taxanes neoadyuvance	
Yes	16 (29.6%)
No	38 (70.4%)
Taxanes adyuvance	
Yes	27 (50%)
No	27 (50%)
HER2 655 Polimorfism:	
AA	30 (55.56%)
AG	22 (40.74%)
GG	2 (3.7%)

Table 1. Baseline characteristic of the patients included in the study



MATERIALS AND METHODS

- 54 patients with HER2 positive breast cancer treated with Trastuzumab in our hospital were evaluated prospectively from January to December 2012.(Table 1)
- Trastuzumab was administered as a loading dose of 8 mg/kg followed by 6 mg/kg every three weeks.
- Cardiac function (left ventricular ejection fraction, LVEF) was checked at baseline and every 3 months by echocardiogram or MUGA (multigated blood-pool imaging) scan. We considered cardiac toxicity when LVEF drops 10 percentage points from baseline and below 50%, decrease of 15% respect to FEVI baseline or any decrease resulting in LVEF<45% at least one during the treatment or clinical manifestation.
- For genotyping we used TaqMan probes and allelic discrimination technique.
- Statistical analysis was performed with SPSS software packages and the level of significance was indicated by a p value lower than 0.05.

RESULTS

Of all patients, 12 developed cardiotoxicity during the treatment with trastuzumab: 4 with genotype AA, 8 with AG and none with GG. (Table 2)

Cardio-toxicity	Tumoral status	FEVI baseline (%)	Time to appearance (months)	Lower FEVI	Time to recovery (months)	Treatment stopped	Relapse after treatment restart
Sintomatic	IIA	65	9	54	1	Yes	Yes
	IIB	53	9	53	No recovery	Yes	No restart
Asintomatic	IIIA	75	6	52	3	Yes	No
	IIA	65	3	45	3	Yes	Yes
	IIIA	ND	6	42	2	Yes	Yes
	IV	52,4	6	41,6	1	Yes	No
	IV	53,6	6	44,3	2	Yes	No
	IIA	53	3	46,1	3	No	-
	IA	70	3	49	3	Yes	No
	IIB	78,7	3	62	3	No	-
	IA	71	12	59	2	No	-
	IA	60	6	50	2	No	-

Table 2. Clinical characteristics of patients with cardiac toxicity and evolution during the treatment

Significant correlation was not found between genotypes AA (vs AG+GG) or GG (vs AA+AG) and cardiac disfunction. Instead, statistically significant differences were shown when comparing patients with genotype AG and AA+GG with cardiotoxicity (p= 0.039, OR= 4.0 95% CI= (1.03-15.60). If we adjusted the p-value according menopausal status at baseline this association was even stronger, (p=0.023, OR=5.12, CI= (1.17-22.45) (Table 3)

Genotype	CARDIOTOXICITY	non-CARDIOTOXICITY	OR (95% CI)	P-value
A/A	4 (33.3%)	26 (61.9%)	0.35 (0.09-1.28)	0.078
A/G-G/G	8 (66.7%)	16 (38.1%)		
G/G	0 (0%)	2 (4.8%)	0 (0.0-NA)	0.18
A/A-A/G	12 (100%)	40 (95.2%)		
A/G	8 (66.7%)	14 (33.3%)	4.00 (1.03-15.60) 5.12 (1.17-22.45)*	0.039 0.023*
A/A-G/G	4 (33.3%)	28 (66.7%)		

Table 3. HER2 655 A/G genetic variant in cardiotoxicity and non-cardiotoxicity event adverse in HER2 breast cancer patients treated with trastuzumab.
*p-value adjusted by menopausal status

CONCLUSIONS

The results of our study show an association of ERB2 polymorphism Ile655Val with cardiac toxicity associated with trastuzumab. Patients with genotype AG have higher risk of developing cardiac disfunction related to trastuzumab than those ones with AA or GG. We need more studies on this polymorphism as well as larger sample sizes to confirm these findings.

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