EVOLUTION OF ACID ZOLEDRONIC IN NEOADJUVANT TREATMENT COMBINNED WITH CHEMOTHERAPY BASED IN ANTHRACYCLINE FOLLOWED BY TAXANE IN LOCALLY ADVANCED BREAST CANCER: ZO-NAnTax

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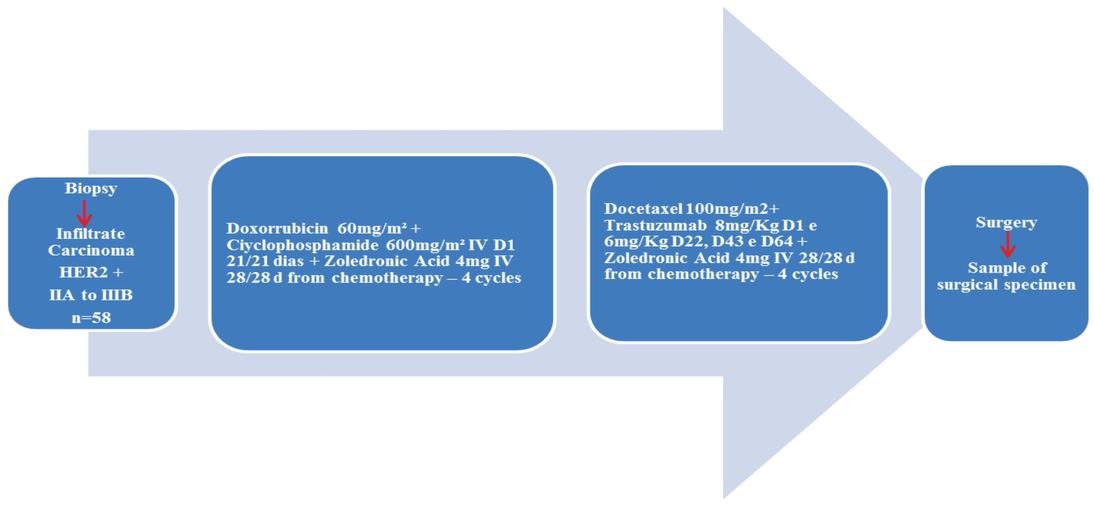
INTRODUCTION

Despite major technological advances, breast cancer remains a big public health problem. It is essential to improve therapeutic individualization, either through better knowledge of action mechanism or the potential synergism between drugs already known that may have an impact on survival, with lower toxicity and lower cost. So, that's why we developed this translational project with the objective of evaluating the efficacy of neoadjuvant treatment of HER2 positive breast cancer patients stage IIA to IIIB, adding zoledronic acid to standard anthracycline treatment followed by taxane with trastuzumab.

OBJECTIVES

Evaluate the efficacy of neoadjuvant treatment of HER2 positive breast cancer patients stage IIA to IIIB, adding zoledronic acid to standard anthracycline treatment followed by taxane with trastuzumab, through the rate of pathological response and correlating it with the molecular profile by immunohistochemistry, with differential gene expression of tumors, inhibition of angiogenesis and with alteration of adhesiveness.

STUDY DESIGN



RESULTS

1) Baseline demographic and clinical characteristics of all systemically treated patients

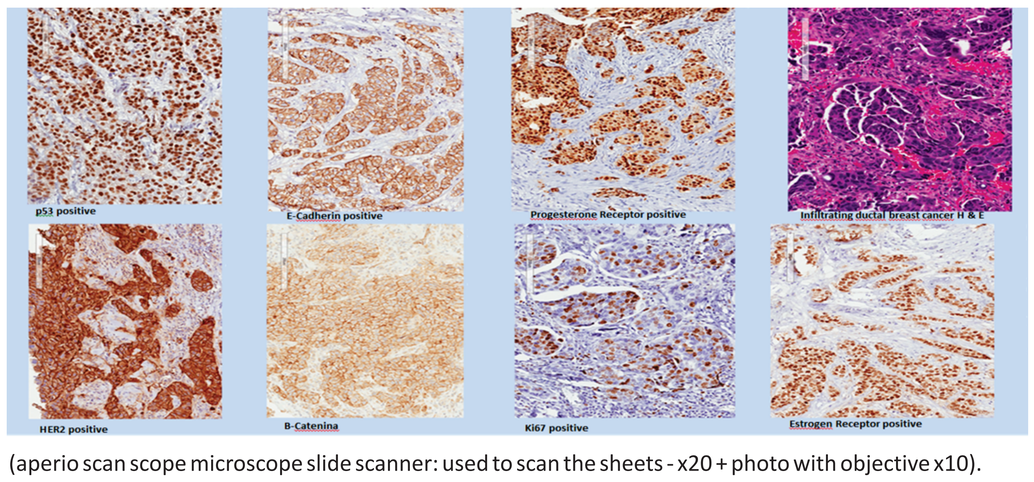
Characteristics	n%
Number of patients included	60 (100)*
Age in years	
median	54 (26 – 74)
Initial tumor size in mm	
median	61 (15 – 120)
Axillary involvement	
N0	29 (48.3)
N1 + N2	31 (51.7)
Staging	
I	0
IIA	11 (18.3)
IIB	22 (36.7)
IIIA	10 (16.7)
IIIB	17 (28.3)
Family history of cancer	
Any cancer	13 (21.7)
Breast / ovarian cancer	16 (26.7)
No history	31 (51.6)
Ethnicity	
White	25 (41.7)
Black	12 (20.0)
Brown	23 (38.3)

* Included patients who underwent systemic treatment and N is the number of axillary lymph nodes compromised according to the TNM classification.

Characteristics	n%
Number of patients included	60 (100)*
Histological Type	
CDI	60 (100)
CLI	0
Others	0
Histological Grade	
G1	0
G2	29 (48.3)
G3	31 (51.7)
Hormonal Receptors	
RE e P positive	28 (46.7)
RE ou P positive	14 (23.3)
RE e P negative	18 (30.0)
HER2	
Positive by IHQ/FISH	60 (100)

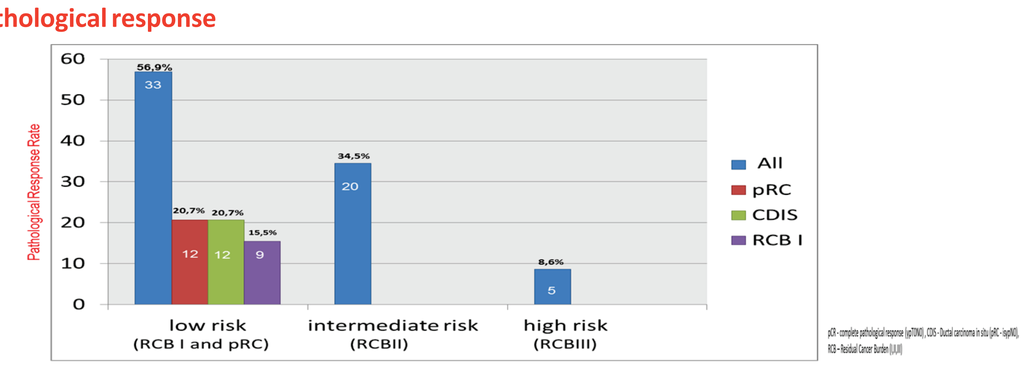
* Included patients who underwent systemic neoadjuvant treatment. CDI - Ductal Infiltrating Carcinoma, CLI - Lobular Infiltrating Carcinoma; RE - Estrogen Receptor, P - progesterone, HER2 - Human Epidermal growth factor Receptor - type 2, IHC - Immunohistochemistry, FISH - Fluorescence in situ hybridization.

2) Molecular markers of prognosis in breast biopsy: Histological sections of the study patients



(aperio scan scope microscope slide scanner: used to scan the sheets - x20 + photo with objective x10).

3) Pathological response



pCR - complete pathological response (ypTONO), CDIS - Ductal carcinoma in situ (ypNC - ypN0), RCB - Residual Cancer Burden (I,II,III)

4)Biological and molecular markers of prognosis on breast biopsy

Biological Characteristics	n%
Number of patients included	58 (100)*
Angiolymphatic invasion	
Present	3 (5.2)
Lacking	55 (94.8)
Perineural infiltrate	
Present	2 (3.4)
Lacking	56 (96.6)
Necrosis	
Present	12 (20.7)
Lacking	45 (77.6)
Remaining result	1 (1.7)
Lymphoplasmacytic Infiltrate	
Present	26 (44.8)
Lacking	31 (53.5)
Remaining result	1 (1.7)

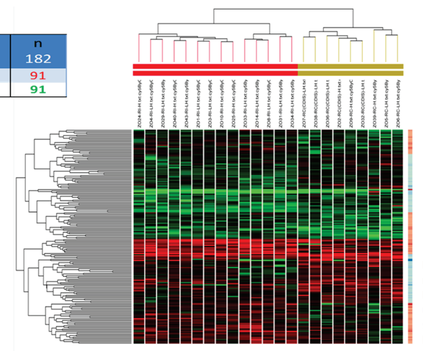
Molecular Characteristics	n%
Number of patients included	58 (100)*
Ki67	
<15%	4 (6.9)
≥15≤20%	5 (8.6)
>20%	49 (84.5)
p53	
≤10%	24 (43.3)
>10<50%	5 (8.6)
≥50%	25 (43.1)
Remaining result	4 (6.9)
β catenina	
Marking:	
Strong membrane	33 (56.9)
Moderate membrane	14 (24.1)
Poor membrane	6 (10.3)
Remaining result	2 (3.4)
	3 (5.2)
E-caderina	
Positive	55 (94.8)
Negative	0
Remaining result	3 (5.2)

* Included patients who underwent neoadjuvant systemic treatment

5) Differential gene expression of patients who had pRC to treatment versus those with residual disease

DIFFERENTIALLY EXPRESSED GENES ALL	n 182
Increased genes	91
Decreased genes	91

Clustering of the 182 differentially expressed genes found in the microarray assay. For this trial, 23 samples were used, of which 9 were from patients with pCR at treatment and 14 from patients who had residual disease. In red the genes increased and in green the diminished ones.



RC-complete response; RI-incomplete response; DCIS-ductal carcinoma in situ; RC (CDIS) - complete response with CDIS, Z-samples from the Zo-NAnTax study; H-subtype HER, LH-subtype luminal HER.

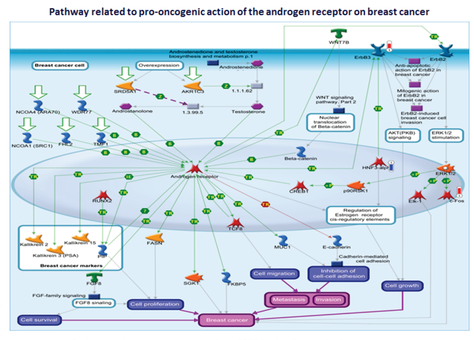
Report of the analysis of the 10 main signaling pathways, where the differentially expressed genes found in the microarray are inserted.

Enrichment analysis report — Complete Response (All) X Incomplete Answer Change Change 1.5 X: Metacore

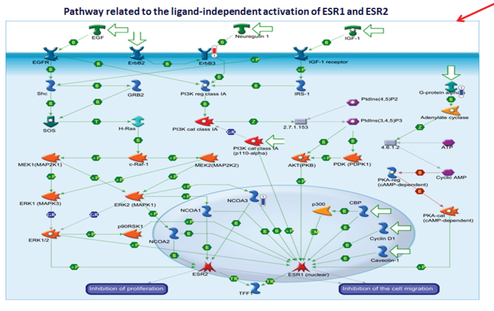
Enrichment by Pathway Maps

#	Maps	Total	pValue	Min FDR	p-value	FDR	In Data	Network Objects from Active Data
1	NETosis in SLE	31	1.855E-05	7.720E-03	1.855E-05	7.720E-03	4	Histone H2A, Histone H2, Histone H4, Histone H1
2	Development_G-protein-mediated regulation of MAPK-ERK signaling	48	9.084E-05	1.617E-02	9.084E-05	1.617E-02	4	GNF, c-Fos, G-protein alpha-s, G-protein alpha-12 family
3	Transcription_N-CoR/SMRT complex-mediated epigenetic gene silencing	49	1.166E-04	1.617E-02	1.166E-04	1.617E-02	4	Histone H2B, Histone H4, c-Fos, TBLR1 (DC42)
4	Development_Activation of astrocytic cells proliferation by ACM3	33	6.502E-04	6.442E-02	6.502E-04	6.442E-02	3	ErbB3, G-protein alpha-13, PLD2
5	Pro-oncogenic action of androgen receptor in breast cancer	35	7.743E-04	6.442E-02	7.743E-04	6.442E-02	3	ErbB3, c-Fos, HNF3-alpha
6	Development_Ligand-independent activation of ESR1 and ESR2	44	1.516E-03	9.616E-02	1.516E-03	9.616E-02	3	ErbB3, G-protein alpha-s, NCOA3 (pCIP/SRC3)
7	Development_Membrane-bound ESR1 interaction with growth factors signaling	45	1.618E-03	9.616E-02	1.618E-03	9.616E-02	3	ErbB3, c-Fos, NCOA3 (pCIP/SRC3)
8	Development_Thromboxane A2 signalling pathway	59	2.194E-03	1.074E-01	2.194E-03	1.074E-01	3	G-protein alpha-s, G-protein alpha-13, G-protein alpha-12 family
9	Signal transduction_PKA signaling	51	2.323E-03	1.074E-01	2.323E-03	1.074E-01	3	G-protein alpha-s, G-protein alpha-13, G-protein alpha-12 family
10	Membrane-bound ESR1 interaction with G-proteins signaling	54	2.737E-03	1.138E-01	2.737E-03	1.138E-01	3	c-Fos, G-protein alpha-s, GPR30

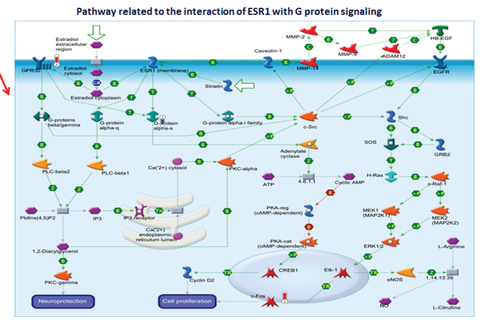
Pathway related to pro-oncogenic action of the androgen receptor on breast cancer



Pathway related to the ligand-independent activation of ESR1 and ESR2



Pathway related to the interaction of ESR1 with G protein signaling



6) Perspectives

- Evaluation of angiogenesis inhibition by quantifying serum VEGF levels in patients' plasma before start treatment and before each cycle of chemotherapy;
- Finalization of molecular data analysis;
- Validation of the results obtained in the microarray assay using real-time polymerase chain reaction (PCR) assays (RT-qPCR) in the all patients samples
- Evaluation of the clinical and pathological variables impact on pathological response rates;
- Verify the effect of experimental treatment on cell adhesiveness.

Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA