Identification of polymorphisms associated with adverse reactions to chemotherapy for breast cancer

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- The reactions may be associated with the treatment, the tumor characteristics and the clinic and genetic patient historic. In particular with the SNPs(Single Nucleotide Polymorphisms) which consist of the modification of a single nucleotide.
- Identify patient profiles and types of treatment related to severe reactions may assist in public policies that improve the life quality of patients.

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- FAC-D is a chemotherapy protocol consisting of 6 cycles 3 cycles ciclofosomida, dexorrubicina and 5-fluoroural followed by 3 cycles of docetaxel.

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- The cohort included 166 women submitted to the FAC-D chemotherapy and the cohort were followed through interviews for evaluation of adverse reactions.
- To classify the severity of the reaction, we used the criteria of the National Cancer Institute (USA): Common Terminology Criteria Adverse Events (CTCAE), in which the reactions are graded in severity levels associated with mild reactions (1), moderate (2), incapacitating (3), severe (4) and fatal (5).

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- The polymorphisms included were: CYP2B6(G15631T), CYP2B6(A18053G), CYP3A5(A6986G), ABCB1(C1236T), ABCB1(C3435T), GSTP1(ILE105VAL), CBR3(G11A), SLCO1B3(IVS12-A5676G).

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- The R (2.3 and 2.15) software was used for analyzes. The GEEPACK package to fit the GEE. The predictors for the marginal was identified using the Wald test.

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- $k = 1, ..., c-1$, (c-categories number), $t = 1, ..., t_i$.

Results

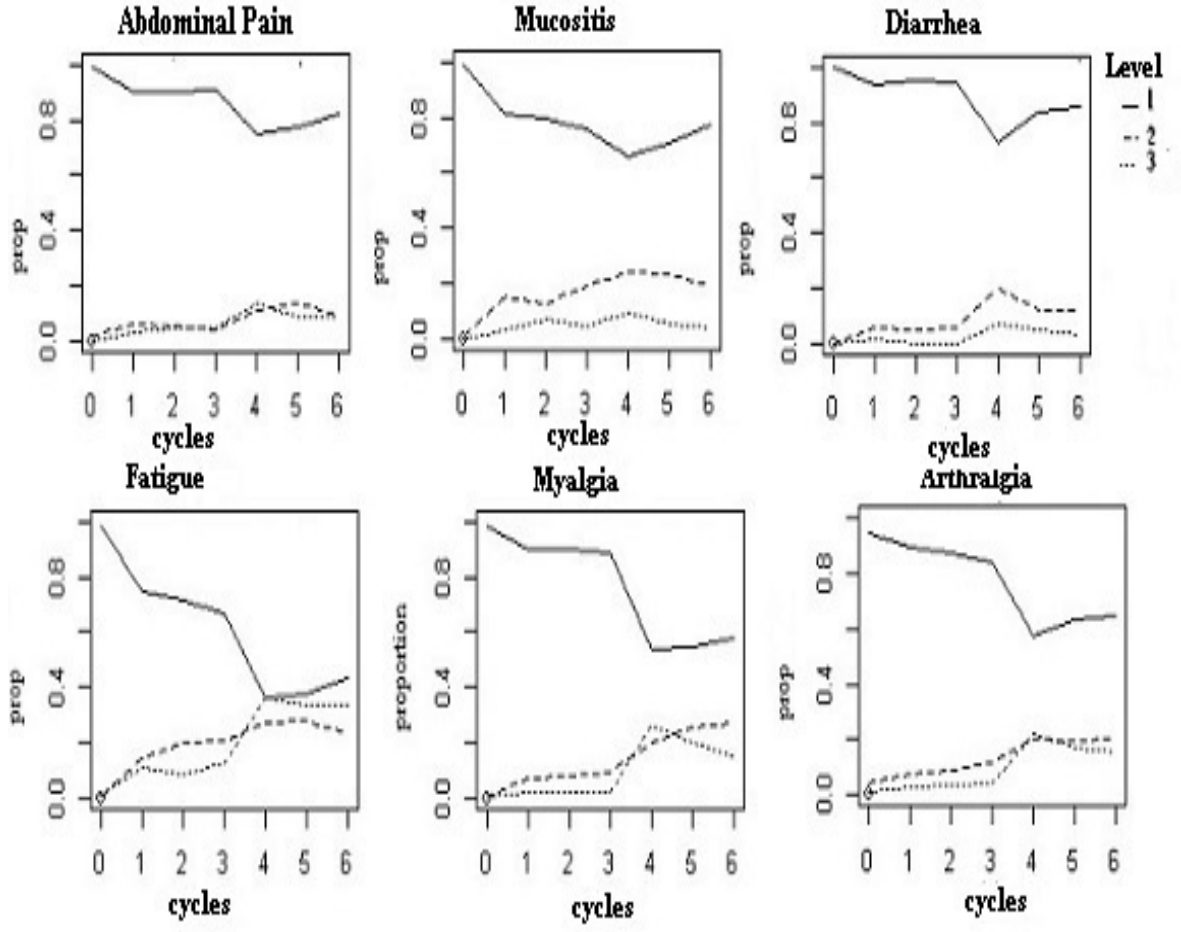
The observed frequency of at least one polymorphism was more common, except for SLCO1B3:

Polimorphisms - (observed frequency)

	number of variant alleles							
Polimorphisms	0(1)		1(2)		2(2)		Not reported	
	n	%	n	%	n	%	n	%
CYP2B6(15631G>T)-CYP2B61	66	39.7	59	35.5	14	8.4	27	16.3
CYP2B6(18053A>G)-CYP2B62	54	32.5	60	36.1	35	21.1	17	10.2
CYP3A5(6986A>G)-CYP3A5	9	5.4	55	33.1	92	55.4	10	6
ABCB1(C1236T)-ABCB11	59	35.5	70	42.2	21	12.6	16	9.6
ABCB1(G2677T|A)-ABCB12	70	42.2	56	33.7	21	12.6	19	11.4
ABCB1(C3435T)-ABCB13	54	32.5	69	41.6	32	19.3	11	6.6
GSTP1(A>GILE105VAL)-GSTP11	65	39.1	73	44	20	12	8	4.8
CBR3(11G>A)-CBR3	54	32.5	69	41.6	23	13.8	20	12
SLCO1B3(A>G)-SLCO1B3	117	70.5	35	21.1	2	1.2	12	7.2

Results

The proportions of women who reported severe levels fatigue, myalgia, arthralgia, abdominal pain, mucositis and diarrhea increased in last chemotherapy cycles:



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- Final model - fatigue:

$$log(\frac{\pi_2 + \pi_3}{\pi_1}) = -0.94 + 1.37x_1 \quad (1)$$

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- where $x_1 = 1$ is the Docetaxel medicament and $x_1 = 0$ is the Fac medicament.

Longitudinal Study

The medicament was significant for all reactions. The ABCB11 polymorphism was associated with lower odds for higher myalgia.

Predictors in longitudinal model

Reactions	Predictors	Estimate	OR	p-valor
Fatigue	Medicament(1)	1.37	3.93	10^{-6}
Myalgia	Medicament(1)	2.21	9.11	10^{-5}
	ABCB11(1)	-1.05	0.35	0.043
Arthralgia	Medicament(1)	1.36	3.89	10^{-4}
Abdominal Pain	Medicament(1)	2.22	9.2	0.003
Mucositis	Medicament(1)	1.33	3.78	0.04
Diarrhea	Medicament(1)	1.8	6.04	0.03

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- Our data showed an increase in the severe levels proportions for reactions during cycles of Docetaxel phase compared to the cycles of FAC phase. This result meets some studies reporting increased toxicity treatment with Docetaxel in other protocols (Hainsworth and Burstein, 1998)
- Marginal models showed that Docetaxel is associated with higher odds for greater reactions levels when compare which the FAC phase. Furthermore, the presence of ABCB11 polymorphisms was associated with lower odds for greater myalgia levels.

Future Work

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- We also intend to perform sensitivity analysis and residual analysis to check the model fit.


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