



Association between genetic, adverse events and pharmacokinetics in testicular cancer patients



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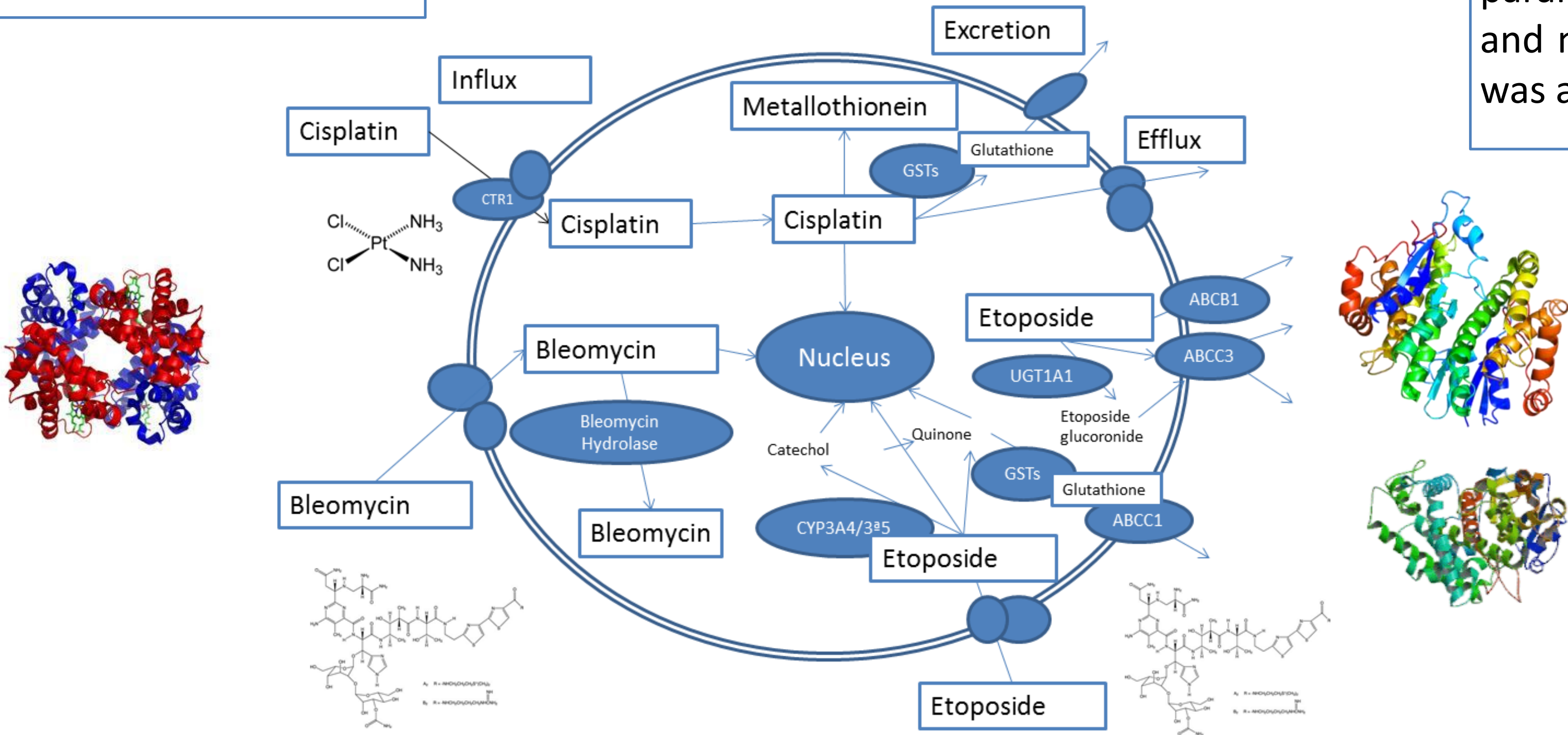
INTRODUCTION: Individual variability in drug efficacy and toxicity resulting in different clinical responses is common in oncology. The antineoplastic drugs often produce toxicity in doses near to those that are needed for the therapeutic effects. Due to the fact that the majorities of the antineoplastic drugs are cytotoxic for nature and have little specificity, the ideal dose presents a narrow range. It is an important problem in clinical practice because it can lead to therapeutic failure and adverse effects. A wide variety of factors may influence drug availability and drug response, such as race, sex, diet, differences in drug pharmacokinetics and pharmacodynamics, etc.

OBJECTIVES: To study the association of the genetics variants, pharmacokinetics of PEB chemotherapy and adverse events related with chemotherapy.

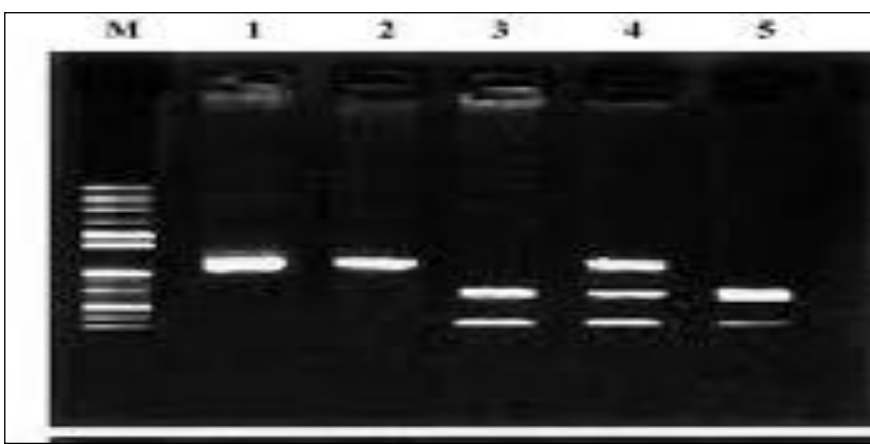
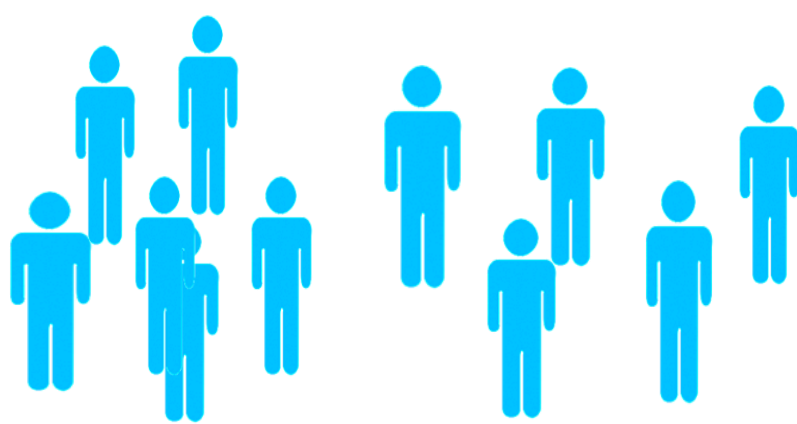
METHODS:

We recruited 63 patients with testicular cancer. Patients were treated with cisplatin, etoposide and Bleomycin (PEB). Genetics polymorphisms on *GSTM1 null*, *GSTT1 null*, *CYP3A4*1B* and *BLMH (A1450G)* were detected in these patients through PCR-RFLP ¹. A pharmacokinetics preliminary study of cisplatin was realized on 9 patients. Analysis statistical was performance with STATA 11.1 and pharmacokinetics data was analyzed with Monolix 4.2 (parametric) ² and Pmetrics (non parametric) ³. Association between polymorphisms and toxicity was investigated using univariate and multivariate logistic regressions and with PK parameters using Mann Whitney tests. The study was approved by scientific and ethical committee of S.S.M.N., Santiago, Chile.

RESULTS

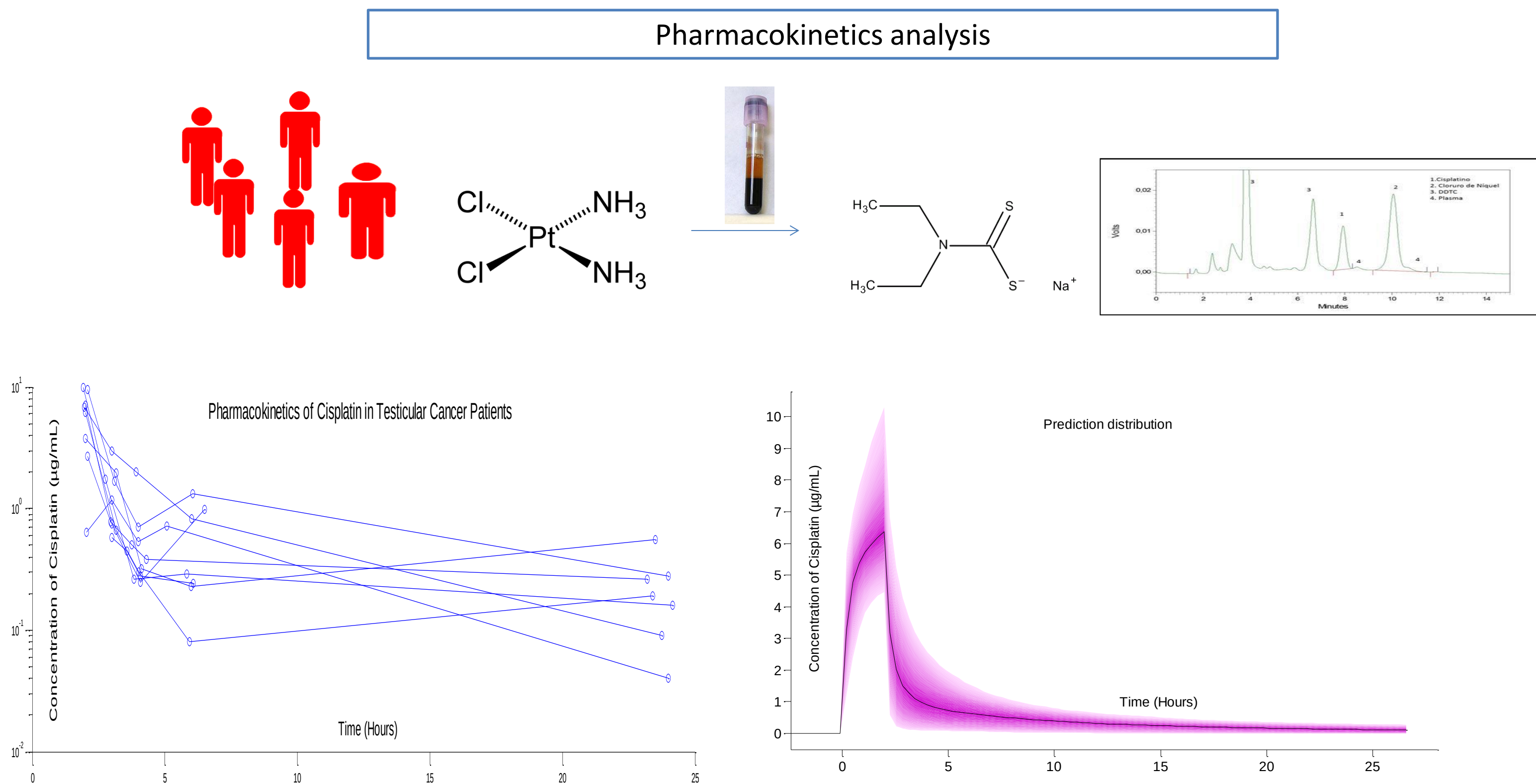


Assotiation genetic variants – adverse events (n=63)



Baseline characteristics of patients		
	n=63	%
Age, years		
Median	30.5	
Range	18-63	
BSA, m ²		
Median	2.0	
Range	1.3-2.3	
Histologic type		
Seminoma	14	22.2
No Seminoma	48	76.2
Other	1	1.6
Chemotherapy		
PE (cisplatin, etoposide)	8	12.7
PEB (cisplatin, etoposide, bleomycin)	52	84.1
Other	3	3.2

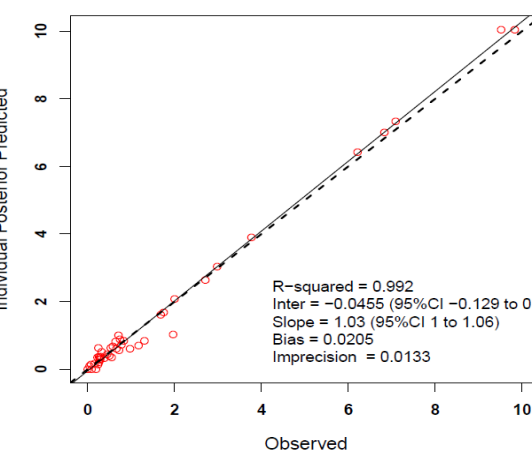
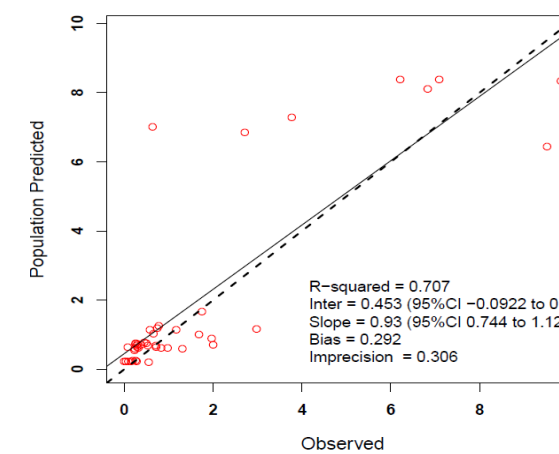
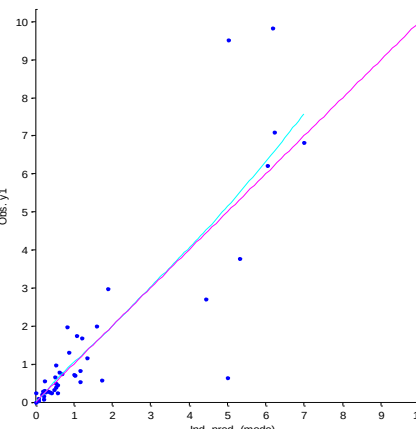
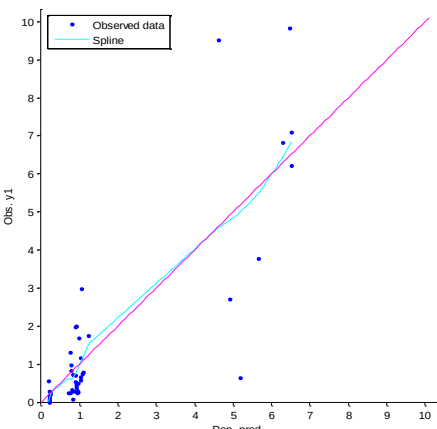
Genotypic and allelic frequency					
<i>CYP3A4*1B</i>		Genotype (n=61)		Allelic	
Frequency	wt/wt	wt/*1B	*1B/*1B	f wt	f *1B
No. (%)	56 (91.8)	5 (8.2)	0	0.959	0.041
<i>GSTM1(-)</i>		Genotype (n=63)		Allelic	
Frequency	wt/wt	(-)/(-)		f wt	f (-)
No. (%)	34 (54.0)	29 (46.0)		0.54	0.46
<i>GSTT1(-)</i>		Genotype (n=62)		Allelic	
Frequency	wt/wt	(-)/(-)		f wt	f (-)
No. (%)	60 (96.8)	2 (3.2)		0.968	0.032
<i>BLMH (A1450G)</i>		Genotype (n=52)		Allelic	
Frequency	A/A	A/G	G/G	f A	f G
No. (%)	28 (53.8)	24 (46.2)	0	0.77	0.23



Model pharmacokinetic: 2 compt
Covariates: BSA, Weight, Cl creat, Age
N=9 patients

Monolix (Parametric)
Cl = 7.44 ± 1.7 L/hr
V1 = 4.16 ± 3.1 L
Bias = 0.236 ± 1.21

P metrics (non parametric)
Ke = 0.86 [0.003-3.25]
V1 = 6.85 [1.2-50]
Ka = 2.5 [1.4-4.9]
Bias = 0.02 ± 0.50



Significant statistical associations between genotype enzymes, and toxicity						
ADR	Variable	Grade 0-2		Grade 3-4		P value
		N	%	n	%	Fisher exact test
Leucopenia	GSTM1					0.052
	Present	25	73.5	9	26.5	0.041
	Null	27	93.1	2	6.9	
Hematological toxicity	BLMH					0.064
	A/A	26	92.9	2	7.1	0.036
	A/G	17	70.8	7	29.2	
Hematological toxicity	BLMH					0.002
	A/A	23	82.14	5	17.86	0.001
	A/G	9	37.5	15	62.5	

Statistically significantly associations between genotypes and risk of ADR

ADR	OR	95% IC
Leucopenia grade 3-4		
GSTM1		
Present	Reference	
Null	0.20	0.04-1.04
BLMH		
A/A	Reference	
A/G	5.35	0.99-28.89
Hematological toxicity		
BLMH		
A/A	Reference	
A/G	7.67	2.14-27.35

	C _{max} (µg/ml)	AUC (µg h /L)	0-24hr	Clearance (l/h)	<i>GST M1 / GSTT1</i>
Mean	4.466	18136		10.21	+ /+ n=3
Mean	7.623	18656		10.38	- /+ n=3
P value (*)	0.27	0,51		0,82	

*Mann-Whitney U test, n=6 patients, preliminar results of association between GST variants and Cisplatin pharmacokinetics.

CONCLUSION: Our findings show that *GSTM1 present* patients and *BLMH A/G* patients are more likely to develop grade 3-4 leucopenia. Hematological toxicity is more frequent in *BLMH A/G* patients. Nevertheless no association between PK parameters and genetic polymorphisms was shown. This is preliminary evidence in pharmacogenetics of PEB chemotherapy in testicular patients.

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