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IMPACT OF NADPH OXIDASE FUNCTIONAL POLYMORPHISMS IN ACUTE MYELOID LEUKEMIA INDUCTION CHEMOTHERAPY

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BACKGROUND

NADPH oxidase, a key mediator of oxidative cardiac damage and remodeling, **modulates anthracycline** clinical **cardiotoxicity**.

PURPOSE

Single nucleotide **polymorphisms** (SNPs) of NADPH oxidase genes could lead to interindividual **differences in treatment outcome** in acute myeloid leukemia (AML) patients.

METHODS

SNPs: three NADPH oxidase polymorphisms CYBA (rs4673), NCF4 (rs1883112), RAC2 (rs13058338)

Patients: 225 adults of a single center at initial diagnosis from AML, induction with idarubicin plus cytarabine (PETHEMA-LMA 99, 2007 & 2010 trials)

Technique: Sequenom® mass spectrometry–based multiplex genotyping assay

Efficacy: complete remission (CR) vs. partial remission (PR)/resistance (deaths were excluded)

Toxicity: grade 0-1 vs. grade 2-4 (maximum grade of all the specific toxicities), WHO scale

Hematologic toxicity: time to neutropenia and thrombocytopenia recovery since first day of chemotherapy

Statics: linear and logistic regression adjusting for age, gender, ECOG, leukocyte and platelet count at diagnosis (R® version 3.1.2)

RESULTS

Patients: median age 51.1 years (range 16-78 years)

Effectiveness: higher CR rates among patients harboring **variant allele of NCF4 and RAC2** (table1)

Toxicity: toxicities were summarized in table 2. Correlation between SNPs and cardiotoxicity was not found.

TABLE 1. Significant association between NADH oxidase SNPs and effectiveness

Gene/SNP	Genotypes	CR n (%)	Grade 2-4 n (%)	OR (95%CI)	P
NCF4 rs1883112	GG	39(67.2)	19(32.8)	3.19	0.034
	AA	23(85.2)	4(14.8)	(1.16-10.34)	
RAC2 rs13058338	TT	64(65.3)	34(34.7)	2.17	0.036
	TA	41(80.4)	10(19.6)	(1.07-4.63)	

TABLE 2. Significant association between NADH oxidase SNPs and different toxicities

Toxicity	Gene/SNP	Genotypes	Grade 0-1 n (%)	Grade 2-4 n (%)	OR (95%CI)	P
Lung	*CYBA rs4673*	*CC TT*	55(73.3) 27(90.0)	20(26.7) 3(10.0)	0.25 (0.04-0.78)	0.029
Hepatic			41(54.7) 23(76.7)	34(45.3) 7(23.3)	0.29 (0.10-0.74)	0.013
Gastrointestinal			46(61.3) 27(90.0)	29(38.7) 3(10.0)	0.29 (0.095-0.75)	0.016
Skin			46(61.3) 25(83.3)	29(38.7) 5(16.7)	0.36 (0.11-0.90)	0.039
Neurological	*NCF4 rs1883112*	*GG AA*	60(89.6) 25(73.5)	7(10.4) 9(26.5)	2.81 (0.97-10.06)	0.050

SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval

CONCLUSION

Although our study did not reproduce the cardiotoxicity previously related with these SNPs in other malignances, we obtained **novel associations with efficacy and safety** of anthracyclines in AML induction.

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