

Megías Vericat JE^{1*}, Montesinos P², Herrero MJ^{1,3}, Bosó V¹, Moscardó F²,
Rojas L¹, Martínez-Cuadrón D², Aliño S^{1,3,4}, Sanz MA², Poveda JL¹

¹Pharmacogenetic Unit, Medicament Clinical Area, Hospital Universitari i Politecnic La Fe, Valencia, Spain. ²Hematology Department, Hospital Universitari i Politecnic La Fe, Valencia, Spain. ³Clinical Pharmacology Unit, Medicament Clinical Area, Hospital Universitari i Politecnic La Fe, Valencia, Spain. ⁴Pharmacology Department, Medicine Faculty, Valencia University, Spain. On behalf of the PETHEMA cooperative group and Instituto Investigación Sanitaria La Fe. *corresponding author: megias_jua@gva.es

BACKGROUND

X Cytarabine is considered the **most effective** chemotherapeutic agent in **acute myeloid leukemia (AML)** treatment.

PURPOSE

X Several studies suggest that single nucleotide polymorphisms (**SNPs**) in genes involving **metabolic pathway of cytarabine** could **influence in treatment outcomes**, although their clinical relevance remains undetermined.

METHODS

Patients: 225 adults at initial diagnosis from AML, induction with idarubicin plus cytarabine

SNPs: *DCK*:rs2306744, rs11544786, rs4694362; *CDA*:rs2072671, rs3215400, rs532545, rs602950; *NT5C2*:rs11598702; *RRM1*:rs9937; *NME1*:rs2302254

Technique: Sequenom[®] mass spectrometry–based multiplex genotyping assay

Efficacy: complete remission (CR) vs. partial remission (PR)/resistance (deaths excluded); overall survival (OS), event-free survival (EFS), disease-free survival (DFS) and relapse-free survival (RFS) at 5 years

Statics: linear and logistic regression adjusting for age, gender, ECOG, leukocyte and platelet count, hemoglobin, creatinine, bilirubin, albumin and LDH level at diagnosis (R² 3.1.2)

RESULTS

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

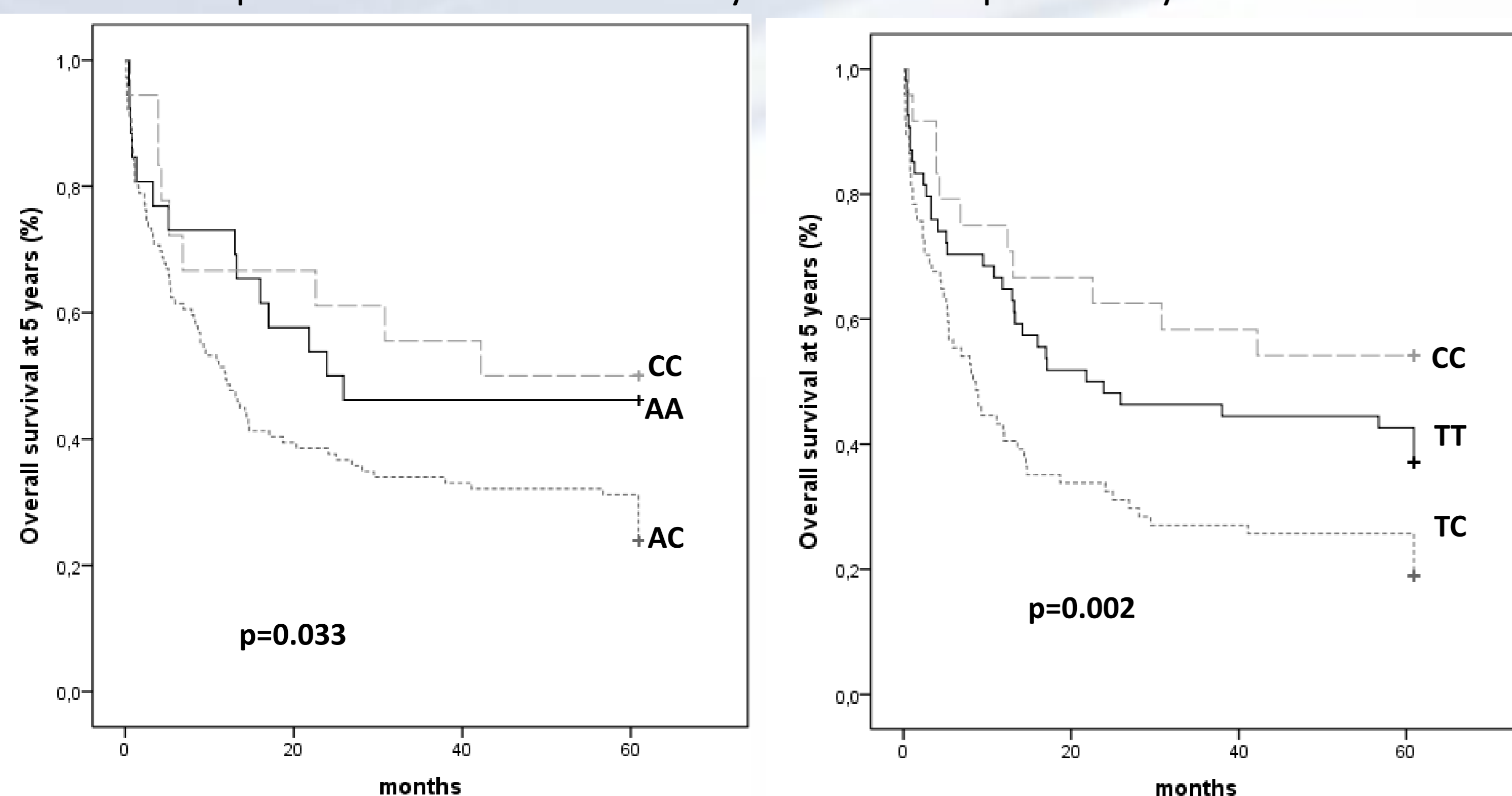
Effectiveness: significant associations were summarized in tables 1-2

TABLE 1. Associations between metabolic Ara C SNPs and efficacy variables.

Variable	Gene/SNP	Genotypes	CR n (%)	non-CR n (%)	OR (95%CI)	P-value
CR	<i>DCK</i> rs2306744	GG	116 (56.6)	89 (43.4)	1	0.024
		GA	15 (83.3)	3 (16.7)	6.2 (1.3-30.2)	
CR	<i>CDA</i> rs602950	TT	46 (57.5)	34 (42.5)	1	NS
		TC	58 (53.7)	50 (46.3)	ND	
		CC	27 (75.0)	9 (25.0)	3.0 (1.02-8.8)	

ND: not determined; NS: non-significant; HR: hazard ratio; OR: odds ratio;

FIGURES 1 & 2. Kaplan-Meier curve of OS at 5 years for AML patients by rs2072671 & rs602950



CONCLUSION

- Influence in **Ara C efficacy of *DCK*, *CDA* and *RRM1* polymorphisms** in AML adult patients, previously suggested in other studies.
- **Novel associations** between SNPs in metabolic Ara C genes were detected.
- Further studies with larger population are needed to validate these associations, which could be **useful biomarkers in clinical practice**.

TABLE 2. Associations between metabolic Ara C SNPs and survival rates.

Variable	Gene/SNP	Genotypes	Non-event n (%)	Event n (%)	HR (95%CI)	P-value
OS at 5 years (FIGURE 1)	<i>CDA</i> rs2072671	AA	12 (46.2)	14 (53.8)	1	0.015
		AC	26 (23.9)	83 (76.1)	2.2 (1.2-4.1)	
		CC	9 (50.0)	9 (50.0)	ND	
EFS at 5 years	<i>CDA</i> rs2072671	AA	11 (42.3)	15 (57.7)	1	0.045
		AC	17 (15.6)	92 (84.4)	1.9 (1.01-3.4)	
		CC	9 (50.0)	9 (50.0)	ND	
DFS at 5 years	<i>CDA</i> rs2072671	AA	11 (73.3)	4 (26.7)	1	0.027
		AC	17 (30.9)	38 (69.1)	3.8 (1.2-12.4)	
		CC	9 (75.0)	3 (25.0)	ND	
RFS at 5 years	<i>CDA</i> rs2072671	AA	11 (84.6)	2 (15.4)	1	0.032
		AC	17 (44.7)	21 (55.3)	9.1 (1.2-68.6)	
		CC	9 (90.0)	1 (10.0)	ND	
DFS at 5 years	<i>CDA</i> rs3215400	DEL/DEL	16 (59.3)	11 (40.7)	1	0.006
		DEL/C	12 (30.8)	27 (69.2)	2.9 (1.4-6.3)	
		CC	9 (56.3)	7 (43.7)	ND	
RFS at 5 years	<i>CDA</i> rs3215400	DEL/DEL	16 (72.7)	6 (28.3)	1	0.033
		DEL/C	12 (48.0)	13 (52.0)	3.3 (1.1-9.9)	
		CC	9 (64.3)	5 (35.7)	ND	
OS at 5 years (FIGURE 2)	<i>CDA</i> rs602950	TT	20 (37.0)	34 (63.0)	1	0.039
		TC	14 (18.9)	60 (81.1)	1.7 (1.03-2.6)	
		CC	13 (54.2)	11 (45.8)	ND	
EFS at 5 years	<i>CDA</i> rs602950	TT	13 (24.1)	41 (75.9)	1	NS
		TC	11 (14.9)	63 (85.1)	ND	
		CC	13 (54.2)	11 (45.8)	0.4 (0.2-0.8)	
OS at 5 years	<i>RRM1</i> rs9937	AA	16 (44.4)	20 (55.6)	1	0.021
		AG	14 (21.5)	51 (78.5)	2.0 (1.1-3.5)	
		GG	17 (32.7)	35 (67.3)	ND	
RFS at 5 years	<i>RRM1</i> rs9937	AA	12 (75.0)	4 (25.0)	1	0.047
		AG	11 (47.8)	12 (52.2)	3.8 (1.02-14.3)	
		GG	14 (63.6)	8 (36.4)	ND	