



Combined interaction of multi-locus genetic polymorphisms in cytarabine arabinoside metabolic pathway on clinical outcomes in adult acute myeloid leukaemia (AML) patients

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Abstract Cytarabine arabinoside (ara-C) is the key agent for treating acute myeloid leukaemia (AML). Here, we genotyped 139 single nucleotide polymorphisms (SNPs) within the ara-C transport and metabolic pathway using the Illumina Golden Gate Assay in 97 patients with previously non-treated *de novo* AML other than M3. *DCK* rs4694362 (CC genotype) was a significant poor prognostic factor for overall survival (OS) (hazard ratio [HR], 33.202 [95% confidence interval (CI), 4.937–223.273], $P < 0.0001$, $P_{\text{Bonferroni}} = 0.017$). *SLC29A1* rs3734703 (AA or AC genotype) in combination with *TYMS* rs2612100 (AA genotype) was significantly associated with shorter relapse free survival (RFS) (HR, 17.630 [95% CI, 4.829–64.369], $P < 0.0001$, $P_{\text{Bonferroni}} = 0.021$). These SNPs showed moderate or large inter-ethnic divergence in allele frequencies from African or Caucasian populations. The results of our study suggest that a single SNP and SNP–SNP interactions may help to predict the drug response and provide a guide in developing individualised chemotherapy for AML patients receiving ara-C based chemotherapy.

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1. Introduction

Cytarabine arabinoside (ara-C) is the key agent for treating acute myeloid leukaemia (AML).^{1,2} However, large inter-individual differences in response and toxicity

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are still major drawbacks. Only 20% to 30% of patients experience a long-term disease-free survival and the majority of patients die primarily of persistent or relapsed AML.³ In addition, multiple trials demonstrated an inter-ethnic difference in treatment outcomes among AML patients receiving the ara-C regimen.^{4–6} However, much of the focus of these inter-individual or inter-ethnic differences in treatment outcomes has focused on Caucasians and Africans with negligible attention being paid to Asians.

As its mechanism of action, ara-C is transported into leukaemic cells by membrane transporters including the solute carrier family 29 (nucleoside transporters) member 1 (SLC29A1).^{7,8} And once it is inside the cell, ara-C is phosphorylated into ara-C monophosphate (ara-CMP) by deoxycytidine kinase (DCK) and eventually to ara-C triphosphate (ara-CTP), which then competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA and subsequently blocking DNA synthesis causing leukaemic cell death.⁹ Other important enzymes are cytidine deaminase (CDA) which catalyses the conversion of ara-C into inactive uracil arabinoside (ara-U), and deoxycytidylate deaminases (DCTD) which catalyses the conversion of ara-CMP into inactive ara-UMP.¹⁰ Each of these genes has been shown to exhibit a significant degree of genetic variation, particularly by single nucleotide polymorphisms (SNPs).^{11,12} However, many studies focusing on an individual SNP have failed to replicate some single locus SNPs playing an important role in the clinical outcomes of AML patients.^{9,12–14} Analysis of the combined effects of SNPs may provide evidence of drug response.^{15,16} These complex gene–gene interactions have been reported as the norm rather than the exception as a risk of common multifactorial human diseases or drug response.¹⁷ Therefore, given the interconnected nature of the drug response, delineating the combined effects of multiple genes acting collectively is an important aspect in explaining why clinical outcomes vary so much between patients.^{16,18}

Therefore, in our quest to identify the susceptible genetic variants affecting the clinical outcomes of AML patients receiving ara-C chemotherapy, both independent SNP and combinations of multi-locus SNPs lying within the ara-C transport and metabolic pathway were determined. In addition, the population specificity in allele frequencies of these SNPs through interethnic comparisons was assessed in this study.

2. Patients and methods

2.1. Study population and their treatment

Ninety-seven patients diagnosed with AML other than M3 and 241 Korean normal controls were included in this study. Subjects who were diagnosed with any other cancer or haematological malignancies or previously

administered cytotoxic drugs or radiation were excluded. Bone marrow or peripheral blood samples were provided from AML patients at diagnosis and normal controls for genotyping. All subjects enrolled in this study provided informed consent for genetic analysis. This study was approved by the Institutional Review Board of Seoul National University Hospital.

All AML patients received an induction regimen consisting of ara-C and idarubicin. A standard dose of ara-C 100 mg/m² for 7 days and idarubicin 12 mg/m² for 3 days was administered to 79 patients, while 18 patients were treated with the modified dose regimen based on their general condition at a physician's discretion. Once patients achieved complete remission (CR), the patients received sequential consolidation therapy consisting of ara-C and anthracyclines or haematopoietic stem cell transplantation (HSCT).

2.2. SNP selection, genotyping and SNP databases

Based on literature searches in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and PharmGKB (<http://www.pharmgkb.org/index.jsp>), we selected 10 genes that were reported as potentially involved in the response to ara-C as follows: five ara-C transport and metabolism genes including *SLC29A1*, *DCK*, cytosolic 5'-nucleotidase III (*NT5C3*), *CDA* and *DCTD*; three drug metabolism genes including cytochrome P450 1A1 (*CYP1A1*), glutathione S-transferase Mu 1 (*GSTM1*) and NAD(P)H dehydrogenase, quinone 1 (*NQO1*); and two folate metabolism genes including methylenetetrahydrofolate reductase (*MTHFR*) and thymidylate synthase (*TYMS*). One hundred and thirty-nine candidate SNPs in these respective genes were initially selected based on the database from NCBI (<http://www.ncbi.nlm.nih.gov/>) and International HapMap project (<http://hapmap.ncbi.nlm.nih.gov/>). SNP genotyping was performed at a multiplex level using the Illumina Golden Gate Genotyping Assay (Illumina Inc., San Diego, CA, United States of America (USA)). Each oligonucleotide (bead type) represents a specific SNP locus. The genotype quality score for retaining data was set to 0.25. The deviation from the Hardy-Weinberg Equilibrium for the SNPs with significant patient numbers was tested using the chi-square test. For pairwise linkage disequilibrium (LD) between the genetic markers, three estimators, *D*, *D'* and *r* were computed. Fifty-five tagging SNPs were finally selected with thresholds of $r^2 > 0.8$ for the analysis. These analyses were carried out using the Hapview 4.2 (Cambridge, MA, USA).

To determine the ethnic differences in allele frequencies of the 139 SNPs between Korean and other populations, the International HapMap database and the 1000 genomes database (<http://www.1000genomes.org/>) were used. For the HapMap data, four populations were selected: Caucasian, Chinese, Japanese and African.

2.3. Evaluation of clinical response and toxicity

The clinical and pathological information of the AML patients was obtained by chart review from the clinical database at the study institution. CR was defined as follows: blast cell counts in the bone marrow <5%; absence of extramedullary disease; absolute neutrophil count $>1.0 \times 10^9/L$; platelet count $>100 \times 10^9/L$.² Relapse was defined as the presence of more than 5% of blast cells in the bone marrow or reappearance of blast cells in the blood or development of extramedullary disease. Relapse free survival (RFS) was measured from the date of achievement of remission until the date of relapse or death from any cause. Overall survival (OS) was measured from the date of entry into the study to the date of death from any cause. Patients who underwent HSCT after their CR were censored at their date of HSCT. Haematologic toxicity during the induction chemotherapy was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.¹⁹

2.4. Statistical analysis

The association of each SNP or combination of SNPs with CR after induction chemotherapy was tested with multiple logistic regression. Survival probabilities were estimated by the Kaplan–Meier method, and differences in the distributions between the genotypes were evaluated using the log-rank test. For multiple regression analysis, a Cox proportional hazard model was constructed for RFS and OS, adjusting for potential confounding covariates including gender, age at diagnosis, subtype, karyotype, complete blood count at diagnosis, bone marrow blast count at diagnosis, *inv(16)(p13q22)*, *t(8;21)(q22;q22)*, *MLL* rearrangement and *NPM1/FLT3* mutation risk status. A stepwise selection method was carried out to determine the potential confounding covariates, which explain the responses well. For SNP analysis, we tested three different genetic models, including the dominant, recessive and additive model. Statistical analyses were carried out with the IBM SPSS software (version 19.0; IBM SPSS Inc., Chicago, IL, USA) and the free statistical computing environment R (version 2.3.1). For all analyses, P values were two-tailed, and a P value of less than 0.05 was considered significant. Multiple test adjustment was additionally performed using the Bonferroni correction.

For interethnic comparison of the minor allele frequency (MAF), F_{ST} and chi-square test were calculated between Korean and other populations.²⁰ We first compared the MAF of the 139 SNPs between Korean AML patients and normal controls, and there were no significant differences between the two groups. Thus, we compared the MAF of all Koreans ($n = 338$) with those of other ethnic groups. Values of F_{ST} less than 0.05

represent low genetic divergence, values between 0.05 and 0.15 are considered to represent moderate divergence, F_{ST} of 0.15 to 0.25 indicates a large divergence and F_{ST} greater than 0.25 represents a very large divergence.²¹ And a P value of 0.005 was considered as the significance level of the chi-square test to judge population differentiation.

3. Results

3.1. Patients' characteristics and treatment outcomes

Baseline characteristics and treatment results of the 97 AML patients are summarised in Table 1. The median age of patients was 50.0 years (range, 16.0–76.0 years) and the male/female proportion was 61/36. The most frequent French–American–British subtype was M2 (49.5%) followed by M4 (27.8%). A total of 48 patients (51.6%) were of normal karyotype. Among the patients who were available for their cytogenetic or molecular information, 21 patients had *t(8;21)(q22;q22)*. Five patients had *inv(16)(p13q22)* and seven patients had *MLL* rearrangement. Of the 79 patients in whom the *NPM1* and *FLT3* internal tandem duplication (ITD) mutation information was identified, 71 patients (91.8%) had a high-risk status.

Overall, 78 patients (88.6%) achieved overall remission after ara-C based induction chemotherapy. Sixty-nine patients (78.4%) achieved CR after their first course of induction therapy, and another nine patients achieved CR after reinduction therapy. Among the 78 patients, 46 patients (59.0%) relapsed during the follow-up period. Median and mean follow-up period for the 97 patients were 10.3 and 22.0 months, respectively (range, 0.6–108.5 months). Fifty-eight patients (59.8%) out of 97 patients died from their disease progression or disease related complications by the end of the follow-up period.

3.2. Single SNP effect on ara-C based treatment outcomes

In the multivariate analysis, SNP rs4694362 in the *DCK* gene, individually, was a significant prognostic factor for OS (Fig. 1a). The CC genotype was significantly associated with less survival time compared to the CT or TT genotypes (hazard ratio [HR], 33.202 [95% confidence interval (CI), 4.937–223.273], $P < 0.0001$, $P_{\text{Bonferroni}} = 0.017$). However, none of the 55 SNPs, individually, had any associations with the achievement of CR after the induction chemotherapy or RFS after adjusting for multiple testing.

3.3. Combined effects of SNPs on ara-C based treatment outcomes

SLC29A1 rs3734703 and *TYMS* rs2612100 were the multi-locus genotype combination that best explained

Table 1
AML patients' characteristics and treatment outcomes.

Characteristics	Σn	n	%	Median (range)
Gender	97			
Male/female		61/36	62.9/37.1	
Age (years)	97			50.0 (16.0–76.0)
FAB classification	97			
M0		2	2.1	
M1		13	13.4	
M2		48	49.5	
M4		27	27.8	
M5		5	5.2	
M6		1	1.0	
M7		1	1.0	
Bone marrow blast (%)	89			60.9 (6.8–98.7)
White blood cell ($\times 10^3/\mu\text{l}$)	94			18.0 (1.1–314.5)
Hemoglobin (g/dL)	94			8.2 (4.1–19.4)
Platelet ($\times 10^3/\mu\text{l}$)	94			38.5 (3.0–278.0)
Karyotype	97			
Normal/abnormal		48/45	51.6/48.4	
Inv(16) (p13q22)	45			
Positive/negative		6/39	13.3/86.7	
<i>t</i> (8;21) (q22;q22)	95			
Positive/negative		21/74	22.1/77.9	
<i>MLL</i> rearrangement	85			
Positive/negative		7/78	8.2/91.8	
<i>NPM1/FLT3</i> risk status ^a	79			
Low/high		8/71	10.1/89.9	
Overall remission	88			
Yes/no		78/10	88.6/11.4	
Relapse before HSCT	78			
Yes/no		46/32	59.0/41.0	
HSCT during the F/U period	97			
Yes/no		34/63	25.1/64.9	

Abbreviations: FAB, French–American–British; F/U, follow up; HSCT, haematopoietic stem cell transplantation.

^a *NPM1/FLT3* status: High risk group, *NPM1* wild/*FLT3* ITD(–), *NPM1* wild/*FLT3* ITD(+), *NPM1* mutated/*FLT3* ITD(+); Low risk group, *NPM1* mutated/*FLT3* ITD(–).

the RFS of AML patients receiving ara-C based chemotherapy (Table 2, Fig. 1b). Multivariate analysis of RFS revealed that the *SLC29A1* rs3734703 (AA or AC genotype) in combination with *TYMS* rs2612100 (AA genotype) was significantly associated with shorter RFS compared to the combination with wild type (HR, 17.630 [95% CI, 4.829–64.369], $P < 0.0001$, $P_{\text{Bonferroni}} = 0.021$). The effect of these SNP–SNP interactions also decreased the OS, although not statistically significant after the multiple test adjustment (HR, 23.523 [95% CI, 4.616–119.873], $P = 0.0001$). *CDA* rs10916827 (GG genotype) in combination with *DCTD* rs17331744 (TC or CC genotype) tended to be associated with shorter OS, but it was marginally significant after the multiple test adjustment (HR, 31.680, [95% CI, 6.152–162.905], $P < 0.0001$, $P_{\text{Bonferroni}} = 0.052$) (Fig. 1c). Regarding CR or overall remission, there were no significant combined effects from the SNPs after the multiple test adjustment.

3.4. Effect of SNPs on ara-C based chemotherapy toxicity

None of the 55 SNPs individually or in combination were associated with an experience of febrile neutropenia greater than grade 3, severe neutropenia of grade 4 or duration of severe neutropenia after ara-C based induction chemotherapy. None of the clinical factors were predictive of haematologic toxicities after ara-C based induction chemotherapy.

3.5. Comparison of the MAF of the SNPs between different populations

Overall, MAF of the 139 SNPs in Chinese and Japanese populations was extremely similar to Koreans, with most of the SNPs clustering at low F_{ST} values. However, MAF in the Caucasian or African populations had a large divergence from those of Koreans (Fig. 2). Among all the pair-wise comparisons between

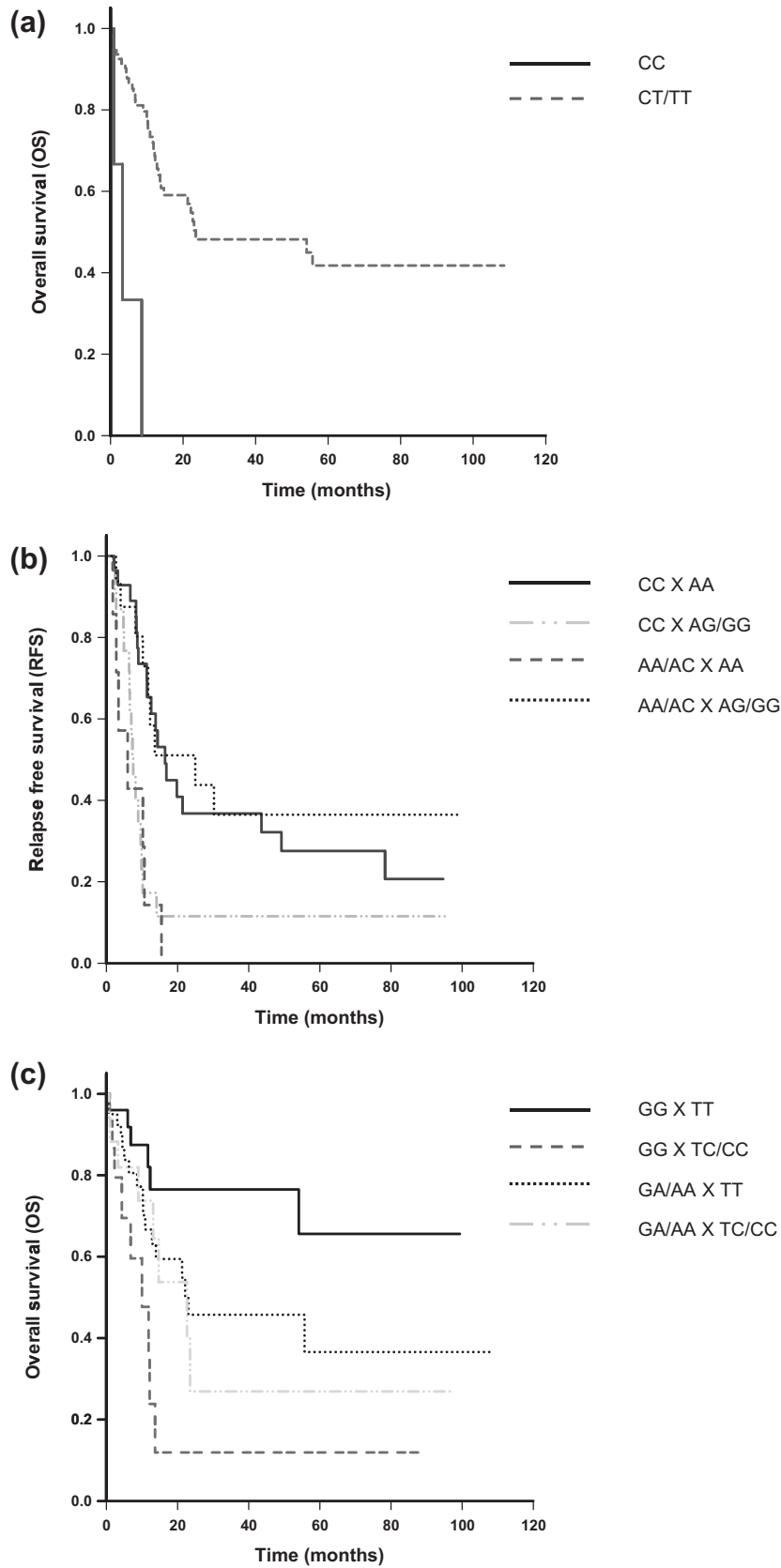


Fig. 1. Significant effect of single SNP or SNP–SNP interactions on relapse free survival (RFS) and overall survival (OS) (a) Single SNP effect of *DCK* rs4694362 on OS (b) Combined effect of *SLC29A1* rs3734703 and *TYMS* rs2612100 on RFS (c) Combined effect of *CDA* rs10926817 and *DCTD* rs17331744 on OS.

Table 2
Significant effect of SNP–SNP interactions on RFS or OS.

Endpoint	SNP–SNP interaction		Genotype	HR (95% CI)	p^b	p^c
RFS ^a	SLC29A1 rs3734703	TYMS rs2612100	CC × AA ($n = 34$)	1		
			CC × AG/GG ($n = 30$)	3.969 (1.689–9.329)	0.002	0.021
			AA/AC × AA ($n = 11$)	17.630 (4.829–64.369)	<0.0001	
			AA/AC × AG/GG ($n = 21$)	0.999 (0.351–2.842)	0.999	
OS ^a	CDA rs10916827	DCTD rs17331744	GG × TT ($n = 25$)	1		
			GG × TC/CC ($n = 15$)	31.680 (6.152–162.905)	<0.0001	0.052
			GA/AA × TT ($n = 40$)	6.374 (1.624–25.021)	0.008	
			GA/AA × TC/CC ($n = 17$)	6.322 (1.056–37.853)	0.043	

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; RFS, relapse free survival; SNP, single nucleotide polymorphism.

^a Dominant model.

^b P value for each genotype combination; Cox proportional hazard model.

^c Statistically significant after the Bonferroni correction.

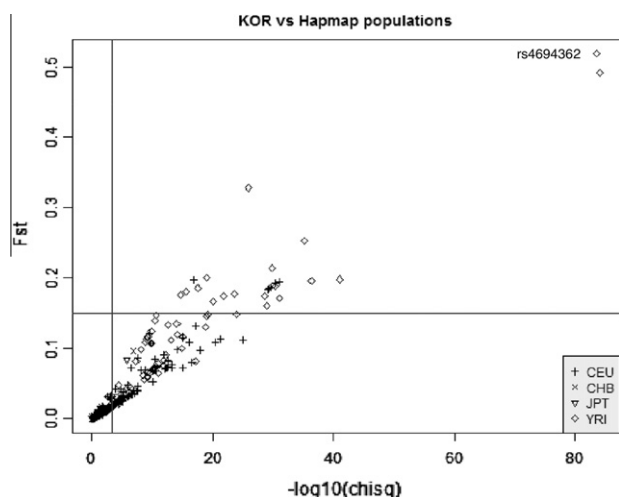


Fig. 2. Overall ethnic difference in allele frequency of 139 single nucleotide polymorphisms (SNPs) in cytarabine arabinoside (ara-C) metabolism pathway. Abbreviations: CEU, Central European; CHB, Chinese; JPT, Japanese; KOR, Korean; YRI, African.

Korean and other populations, *DCK* rs4694362 ranked the highest in F_{ST} for the population comparisons with Africans ($F_{ST} = 0.519$). Other SNPs that have F_{ST} values greater than 0.25 were *MTHFR* rs4846052 (comparison with African, $F_{ST} = 0.492$), *DCK* rs12648166 (comparison with African, $F_{ST} = 0.328$) and *DCTD* rs9542 (comparison with African, $F_{ST} = 0.252$). Among the SNPs which showed a significant relationship with the response to ara-C based chemotherapy in this study, *TYMS* rs2612100 represented a large divergence for the population comparisons with Caucasians ($F_{ST} = 0.195$). *SLC29A1* rs3734703 also showed a moderate difference in MAF compared to Caucasians ($F_{ST} = 0.136$) or Africans ($F_{ST} = 0.136$). However, there were very low divergences of MAF between Korean and other populations for *CDA* rs10916827 and *DCTD* rs17331744 (Table 3).

4. Discussion

Understanding the contribution of the pharmacogenetics to ara-C response could help individualise

chemotherapy and potentially improve outcomes in AML patients. Here, we observed both single SNP and SNP–SNP interactions within the ara-C transport and metabolic pathway, which could account for the inter-patient variability of treatment outcomes in AML patients.

When tested independently, SNP rs4694362 in the *DCK* gene was a significant prognostic factor for OS. The CC genotype was significantly associated with less survival time compared to the CT or TT genotypes. *DCK* is the rate-limiting enzyme which is involved in the activation of ara-C to ara-CTP.⁷ It plays a distinct role in the development of resistance to ara-C, since the *DCK* activity could determine the intracellular ara-CTP concentration and therefore, change the cellular sensitivity.²² Lamba et al. identified a SNP in the 3'UTR region, which is significantly associated with *DCK* mRNA expression and blast ara-CTP concentrations in patients administered ara-C.⁷ Although the meaningful SNP in our study was located in the intron region of *DCK*, it is possible that the clinical effect was probably due to other non-synonymous polymorphisms within the same LD block. In addition, it cannot be ruled out that intronic SNPs may directly regulate transcription by altering RNA elongation, splicing or maturation.^{23,24}

Since the drug response is the result of an interaction of numerous genetic combinations, we strengthened our study by demonstrating the association between the multi-locus polymorphisms within the ara-C transport and metabolic pathway. We specifically demonstrated that the *SLC29A1* rs3734703 AA or AC genotypes in combination with *TYMS* rs2612100 AA genotype are significantly associated with shorter RFS. This combination was also associated with less survival time. As shown in Fig. 3, thymidine triphosphate (TTP) generated by *TYMS* is known to enhance ara-C cytotoxicity by decreasing dCTP pools.²⁵ A decrease in dCTP pools should lead to a relative increase in the amount of ara-C incorporated into DNA since reduction in dCTP levels increases the *DCK* activity, subsequently enhances ara-CTP formation. TTP also inhibits the *DCTD* enzyme which catalyses the conversion of ara-CMP into

Table 3
Interethnic differences in allele frequencies of the important SNPs.

Gene	SNP	KOR–CEU		KOR–YRI		KOR–JPT		KOR–CHB	
		F_{ST}	p -Value ^a	F_{ST}	p -Value ^a	F_{ST}	p -Value ^a	F_{ST}	p -Value ^a
DCK	rs4694362	0.073	<0.0001	0.519	<0.0001	<0.0001	0.996	0.008	0.026
SLC29A1	rs3734703 ^b	0.136	<0.0001	0.136	<0.0001	0.007	0.083	<0.0001	0.871
TYMS	rs2612100	0.195	<0.0001	0.001	0.326	0.004	0.132	<0.0001	0.620
CDA	rs10916827	<0.0001	0.827	0.005	0.074	0.003	0.199	0.002	0.276
DCTD	rs17331744	0.014	0.001	0.016	0.002	<0.0001	0.814	0.0003	0.668

Abbreviations: CEU, Central European; CHB, Chinese; JPT, Japanese; KOR, Korean; YRI, African.

^a P -value from Chi-square or Fisher's exact test.

^b Data from the 1000 genomes project are used for CHB and JPT.

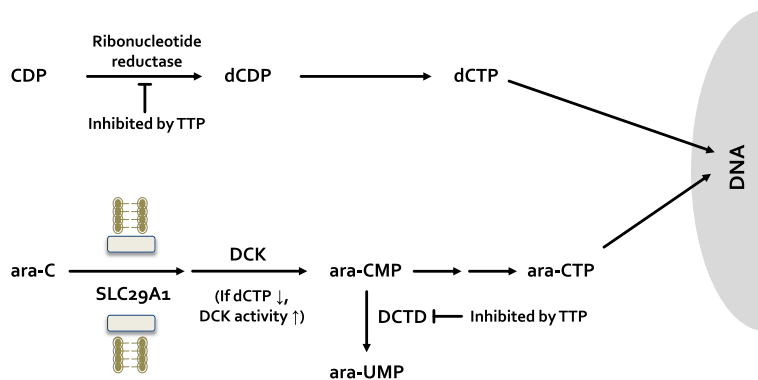


Fig. 3. Combined effect of *SLC29A1* and *TYMS* on cytarabine arabinoside (ara-C) metabolism in blast cells.

inactive ara-UMP. Experimental studies have confirmed that the synergy between ara-C and thymidine occurs in some tumour cell lines^{26,27} and experimental chemotherapy settings.^{28,29} Another SNP–SNP interaction includes *CDA* rs10916827 (GG genotype) in combination with *DCTD* rs17331744 (TC or CC genotype), although this interaction showed a marginal significance for OS. Both *CDA* and *DCTD* are the key enzymes in ara-C degradation.⁹ In pharmacogenomic studies, the effects of combined SNPs play an important role in characterising a trait that involves complex pharmacokinetic and pharmacodynamic mechanisms, particularly when each involved feature only demonstrates a minor effect.³⁰ Here, we have showed that the combination of multi-locus SNPs is a significant genetic factor that can improve the power for detection of genetic effects associated with the treatment outcomes in ara-C based chemotherapy.

In the last few years, there has been great concern that the ethnic difference in the frequency of SNPs involved in the pharmacology is one potential explanation for the differences in treatment outcomes.³¹ The present study showed that the MAF of the 139 SNPs in the Korean population differed greatly from those in Caucasians and Africans but was similar among Asian populations. Especially, *DCK* rs4694362, *SLC29A1* rs3734703 and *TYMS* rs2612100, which were

significantly associated with a response to ara-C based chemotherapy in this study, showed a moderate or large divergence between Korean and African or Caucasian populations.

Our study had some limitations due to the relatively small sample size. In an attempt to examine ara-C toxicities, almost all patients ($n = 88$) experienced febrile neutropenia during the induction chemotherapy and no differences were observed by single or combined genotype analysis. In addition, despite ara-C being the most important drug in AML therapy, patients received a multiagent therapy including anthracyclines in combination with ara-C. Thus, the anthracyclines could have had some influence on the treatment response independent of the examined ara-C related SNPs.

Although AML is a very heterogeneous disease with different subtypes that are of prognostic significance, the results of our study could help in better understanding the effect of a single SNP or SNP–SNP interactions on drug responsiveness and guide us to develop individualised chemotherapy in AML patients receiving ara-C based chemotherapy. Further studies are needed to clearly define the functional role of the SNPs.

Conflict of interest statement

None declared.

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