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No Association of AS3MT Gene Polymorphisms with Susceptibility to Hepatotoxicity in APL Patients Treated with AS2O3: A Single-Center Study

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ABSTRACT

Background: Arsenic three oxide (As2O3) is the treatment choice for acute promyelocytic leukemia (APL). Little is known about possible risk factors with predictive value for toxicity caused by As2O3. Biomethylation is considered to be a major pathway of detoxification for inorganic arsenics (iAs). Arsenic Methyltransferase (AS3MT) is one of the key enzymes involved in the transfer of a methyl group from S-adenosyl-L-methionine to trivalent arsenical and plays a critical role in arsenic detoxification. Polymorphisms in hAS3MT lead to a change in the catalytic activity of the enzyme and may increase the risk of arsenic-related toxicity. In this study, we investigated the association of the AS3MT polymorphisms (rs11191439, rs3740390, and rs3740393) genes with hepatotoxicity in APL patients treated with As2O3.

Materials and Methods: Genotyping was performed in 140 adult patients with APL treated with As2O3 using PCR-RFLP for rs11191439 and tetra-primer ARMS-PCR for rs3740390 and rs3740393. The results of PCR-RFLP and ARMS-PCR were confirmed by direct sequencing of 10 % of DNA samples. The results were analyzed using SNPStats, SPSS, and FinchTV. Hepatotoxicity was graded according to the National Cancer Institute's Common Toxicity Criteria (CTC).

Results: Hepatotoxicity was seen in 52 of the 140 patients (37.1%), with grades I and II hepatotoxicity in 40 (28.6%) and grades III and IV hepatotoxicity in 12 (8.5%) patients. The association between the three polymorphisms and hepatotoxicity was evaluated using five genetic models and none of the three studied polymorphisms were significantly associated with hepatotoxicity.

Discussion: The results of our study showed that AS3MT rs11191439, rs3740390, and rs3740393 polymorphisms are not associated with hepatotoxicity in APL patients. Genetic polymorphisms in enzymes which are involved in arsenic metabolism have been shown to have ethnicity and race-related differences. To more precisely characterize the association between AS3MT gene polymorphism and hepatotoxicity, future large-scale studies in non-Asian populations and other ethnicities are needed.

Keywords: Acute promyelocytic leukemia (APL); Hepatotoxicity; Polymorphism

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INTRODUCTION

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia with a specific molecular marker (PML/RARA). Arsenic trioxide is one of the oldest known drugs that has recently been known to be effective for the treatment of acute promyelocytic leukemia (APL). Therefore, the FDA has expanded the approved use of arsenic trioxide for use in combination with all-trans retinoic acid (ATRA) to treat adult patients with newly diagnosed, low-risk acute promyelocytic leukemia (APL).

When arsenic trioxide [iAs (III); As (2)O (3)] enters the human body, AsV is reduced to AsIII by arsenate reductase, which is then metabolized to monomethylarsonic acid (MMAV) and dimethylarsinic acid (DMAV). These metabolites are then rapidly excreted into the urine[1]. The main detoxification process for IAs (III) is methylation. As Trivalent intermediate metabolites, monomethylarsonous acid (MMAIII) and dimethylarsinous acid (DMAIII) are more toxic than inorganic arsenite[2], individuals with inefficient arsenic methylation capacity may be susceptible to the risk of arsenic cytotoxicity.

Single nucleotide polymorphisms (SNPs) can impact drug plasma concentration, drug detoxification, and drug activation. Genetic polymorphisms influence variability in arsenic metabolism in humans[3]. According to recent research, certain single nucleotide polymorphisms (SNPs) on exons or introns of the AS3MT gene may influence variation in an individual's ability to metabolize arsenic[4]**.**

The AS3MT gene is located on chromosome 10q24.32, spanning approximately 32 kb and containing 11 exons[5]. Twenty-six polymorphic sites in the coding DNA sequence and several intron polymorphisms of AS3MT have been described[5]. rs11191439 is a non-synonymous SNP and characterized by a T→C transition at nucleotide 287 that translates into a Met → Thr substitution at codon 287 in exon 9. The M287T heterozygote on the exons is associated with improved methylation capacity of the AS3MT enzyme[6]. Also, intronic polymorphisms (rs11191439 and rs3740393) were found to have an effect on the As methylation capacity in people who were chronically exposed to arsenic through their drinking water[7,8]. AS3MT polymorphism rs1191439 is correlated with elevated MMA levels in urine, whereas rs3740390 and rs11191453 lead to decreased urinary MMA[9.]

Hepatotoxicity is the major nonhematological toxicity in APL patients who are treated with As2O3[10]. Previous studies have reported hepatotoxicity during APL treatment with AS2O3, with an incidence ranging from 29 to 75 percent[13-15]. In a small number of patients, reversible grade III-IV hepatotoxicity may be observed, leading to the discontinuation of treatment.

A study conducted by Mathews et al. on Indian patients showed that twenty-one (29%) patients developed ATO-induced hepatotoxicity. Seven percent of patients had Grade-3 and four hepatotoxicity[11]. Surprisingly, patients who developed hepatotoxicity had a trend towards a lower risk of relapse. Further, they reported that the homozygous mutant of MTHFR A1298C was associated with hepatotoxicity.

Engström et al. found that AS3MT polymorphisms (rs 3740390 and rs 3740393) were associated with a lower percentage of MMA (%MMA) and a higher percentage of DMA (%DMA) in urine [12].

J Lu et al., in a study that included 50 APL patients treated with As2O3, have shown that DMA % and SMI were significantly negatively associated with the serum levels of ALT and AST [13].

Given that there are significant variations in arsenic metabolism in different individuals that can cause differences in its toxicity, in this study, we retrospectively investigated the association between hepatotoxicity induced by AS2O3 and SNPs in the AS3MT enzyme.

MATERIALS AND METHODS

Patient Enrollment and data collection

The study was approved by the Ethics Committee of Zanjan University of Medical Sciences (Zanjan, Iran) under the Ethics Code of IR.ZUMC.REC.1397.64. APL patients referred to the Hematology, Oncology, and Stem Cell Transplantation Research Center of Shariati Hospital, Tehran, Iran, from 2011 to 2017 were studied.

All the participating individuals in this experiment were of Iranian origin and gave informed consent to participate in this study.

In total, 140 APL patients, including 73 females and 67 males with a median age of 34±13 years (range 15-68 years), were selected based on the availability of patient samples. All the patients had a documented positive PML/RARA RT-PCR test.

Treatment

All patients were treated with single-agent ATO as reported previously[14]. Having obtained signed informed consent from the study participants, we reviewed their medical records. Demographic, clinical, and laboratory data of patients and donors were collected from their medical profiles using a checklist.

Assessment of liver function

Liver function was detected before and during treatment. Hepatotoxicity was considered to be present when ALT and AST levels rose above the upper limits of normality (ULN). During ATO treatments, patients with abnormal liver enzymes, ALT and AST, were defined as having ATO-related hepatotoxicity. The scoring system was according to the National Cancer Institute's Common Toxicity Criteria.

AS3MT polymorphism analysis

Total genomic DNA was extracted from each patient's peripheral leukocyte using a standard salting out method[15]. We selected three SNPs (rs11191439, rs3740390 and rs3740393) in the AS3MT gene. All three polymorphisms are suspected to affect the function of the enzyme[7,8,16]. For rs3740390 and rs3740393, after designing the amplification-refractory mutation system polymerase chain reaction (Tetra-ARMS PCR) primers using Primer1 software[17] the specificity of the primers was checked via a basic local alignment search tool (BLAST) (Table 1). The PCR reaction was carried out in a mixture (20 µl) comprising of 50-100 ng genomic DNA. The conditions of the PCR procedure are listed in Table 2. After that, the amplified PCR products for each SNP were subjected to electrophoresis on a 3% agarose gel. Genotyping of rs11191439 was performed using PCR-RFLP as previously described[18.]

To confirm the tetra-ARMS-PCR genotyping results, DNA sequence analysis was performed on 10% of samples. The forward and reverse outer primers were used in the sequencing procedure. Sequencing was performed using the Big Dye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Foster City, CA, USA). Samples were sequenced following the removal of residual contaminants and unincorporated ddNTPs using an ABI 3130 genetic analyzer (Applied Biosystems). DNA sequences were aligned to reference sequences. The sequencing results were interpreted using the Finch TV software version 1.4.0.

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) was applied to assess the deviation of the genotype or allele frequency. Because continuous variables were distributed abnormally, they were represented by median, and categorical variables were reported as frequency. Data analysis was done using the Pearson's Chi square, Mann–Whitney U-test and t-test in SPSS version 20.0 (IBM, NY, USA).

The association between SNPs and hepatotoxicity was calculated using multiple logistic regression models (codominant, dominant, recessive, over dominant and log-additive) using the SNPStats software and P values of less than 0.05 were considered significant.

Table 1: PCR primers used in the tetra-primer ARMS PCR

SNP ID	Primer set and sequences		Product size (bp)
rs3740390	Fin	CCT TGC ATG TCA TCA GTT ATC TTT ATA	271 bp C allele
	Rin	GTC ATT CAG TAA ATA GAG TGA AGT GAT C	196 bp T allele
	FO	CAT TAG TTC TTT TTC ATG TML TGT AAT	412 bp Control band
	RO	ATG ATT GAA ATG TGG TGA TTA GTA AGT A	
rs3740393	Fin	TTG TTC CCC TAT TML TTT CTT TGT TTT G	G allele 272
	Rin	CAA GAT GAT TAA TGA TTA CAT TGA CCC GAG	C allele 217
	FO	CTG CTT TTG GTT CAG ATT GGC TAA AAA T	Control band 437
	RO	TGC ACA TGT ACA ACC ATC TGC CTT AAT A C	
Fin: Forward inner R in: Reverse inner		FO: Forward Outer RO: Reverse Outer	

Table 2: The condition of PCR procedure

rs3740390	**Tm= 62**℃
Taq DNA Polymerase Master Mix RED (Ampliqon),	7.5µl
Primer Forward Outer	0.4 µl
Primer Reverse Outer	0.4 µl
Primer Reverse Inner	0.6 µl
Primer Forward Inner	1.2 µl
ddH2O	3.9 µl
DNA(50-100 ng)	1 µl
rs3740393	Tm= 64℃
Taq DNA Polymerase Master Mix RED (Ampliqon),	7.5µl
Primer Forward Outer	0.3 µl
Primer Reverse Outer	0.3 µl
Primer Reverse Inner	1.8 µl
Primer Forward Inner	1µl
ddH2O	3.1 µl
DNA(50-100 ng)	1 µl

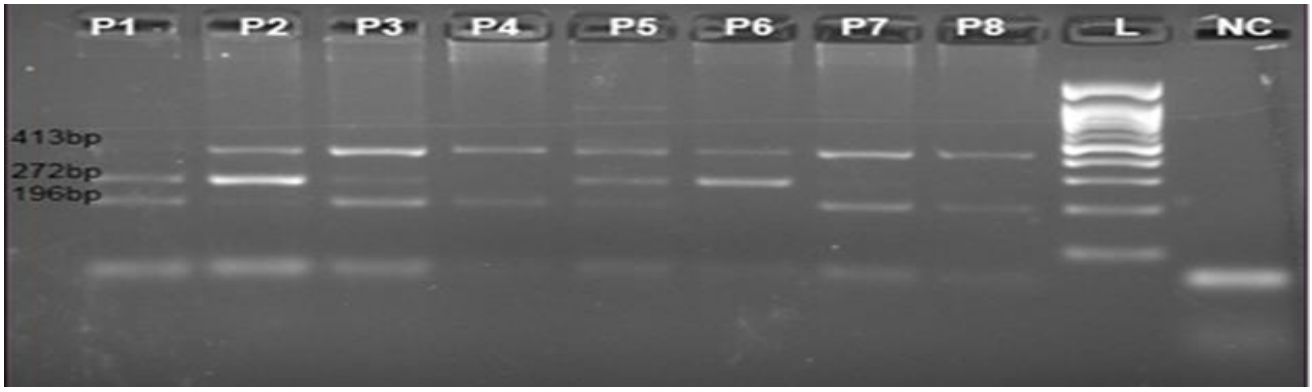

Figure 1A: Electrophoresis pattern of tetra-ARMS-PCR for genotyping of rs3740390. 413 bp band represents the common amplicon, whereas the C and T allele-specific bands are represented by the 272 and 196 bp amplicons, respectively (P: patient, L: 100 bp DNA ladder; NC: negative control).

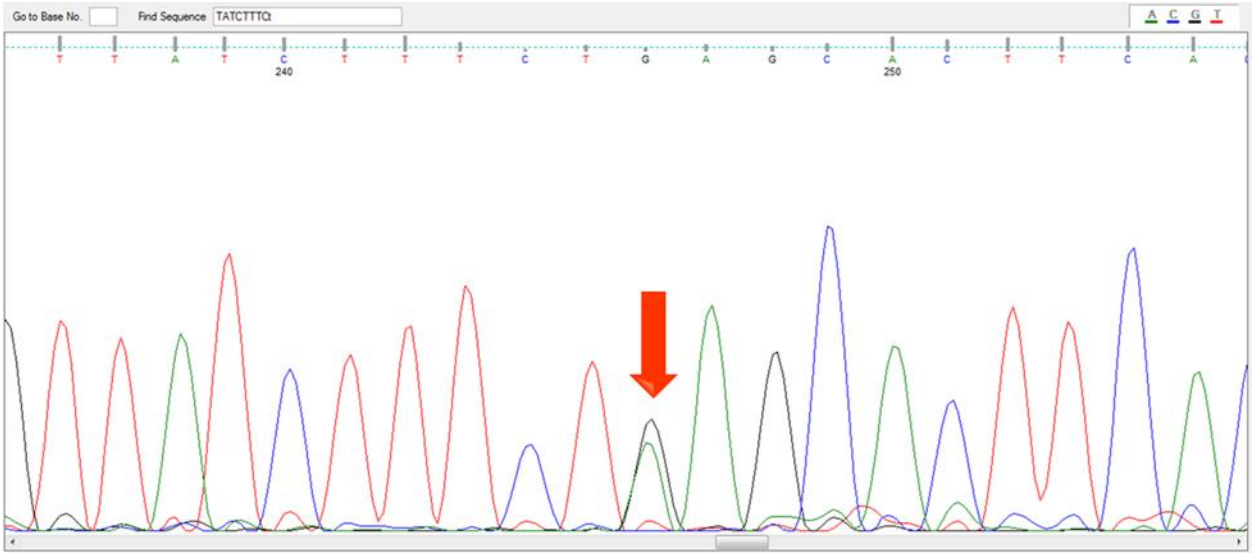

Figure 1B. SNP rs3740390 direct sequencing (by the reverse primer). Representative electropherogram, heterozygote C/T. The red rectangles indicate the SNP position.

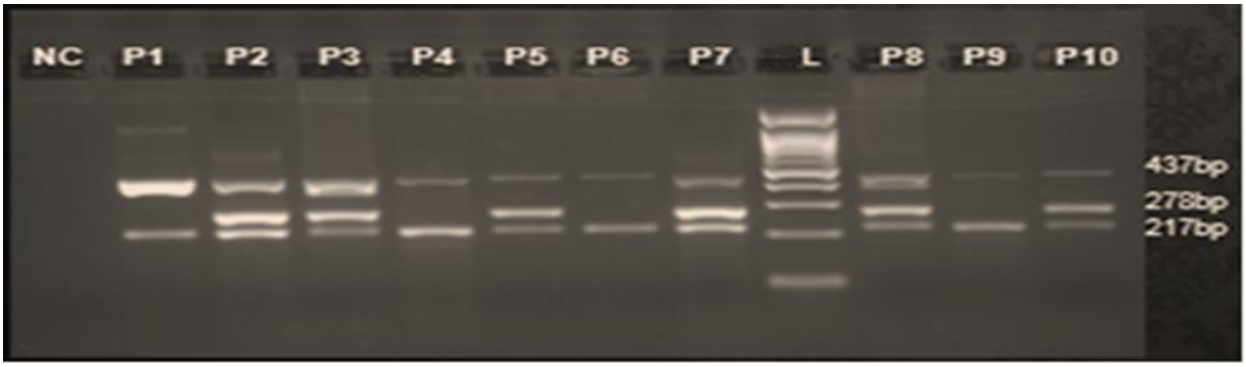

Figure 1C: Electrophoresis pattern of tetra-ARMS-PCR for genotyping of rs3740393. 437 b3p band represents the common amplicon, whereas the G and C allele-specific bands are represented by the 217 and 278 bp amplicons, respectively (P: patient, L: 100 bp DNA ladder; NC: negative control).

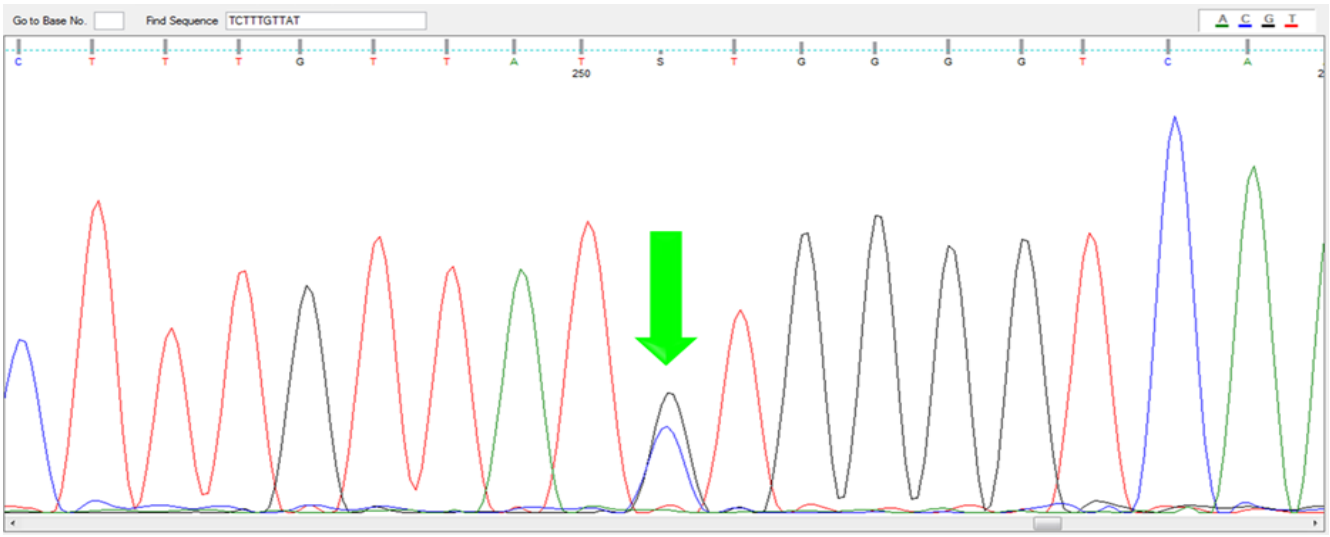

Figure 1D: SNP rs3740393 direct sequencing (by the forward primer). Representative electropherogram, heterozygote G/C. The green rectangles indicate the SNP position.

RESULTS

Patient's characteristics

The study included 140 APL patients (73 females and 67 males) with a median age of 34 years (range: 15-68 years).The demographics and laboratory findings of APL patients are presented in Table 3. There was no significant difference in Sex, age, WBC, PLT, HB and PML/RARA between patients with hepatotoxicity and those without hepatotoxicity.

Distribution of genotype and allele frequency

Figure 1 (A-D) represents electrophoresis and sequencing results. The frequencies of alleles and genotypes for AS3MT SNPs rs11191439, rs3740390, and rs3740393 in APL patients are presented in Table 4. The genotype frequencies of all three SNPs were in Hardy– Weinberg equilibrium (all $P > 0.05$).

Hepatotoxicity was seen in 52 of the 140 patients (37.1%), with grades I and II hepatotoxicity in 40 (28.6%) and grades III and IV hepatotoxicity in 12 (8.5%) patients. There was no history of liver disease, such as viral hepatitis, alcoholic liver disease or autoimmune hepatitis in any of the patients.

We next analyzed the association between AS3MT SNPs and hepatotoxicity in APL subjects. The associations between the polymorphisms in the As3M gene and hepatotoxicity in patients with APL were studied using five genetic models (codominant, dominant, recessive, over dominant, and log-additive). None of the three studied polymorphisms were significantly associated with hepatotoxicity (Table 5).

Table 3: The demographics and laboratory findings of APL patients

Characteristic	APL patients
Median age, years (range)	34(15-68)
Sex, No. (%)	
Male.	67(47.9)
Female	73(52.1)
Median WBC×106/L(range)	270(500-60000)
Median PLT×106/L(range)	41000(4000-470000)
Median Hb g/dL(range)	9.1(4-16)
Hepatooxicity,No.(%)	
No hepatotoxicity	88(62.9)
Grade 1 and 2	40(28.6)
Grade 3 and 4	12(8.5)
PML/RARA isoform, No (%)	
L	84(60)
S	42(30)
V	14(10)

Table 4: Genotypes and allele frequencies of polymorphisms for APL patients

SNP ID	Genotype/Allele	Count (%)	No Hepatotoxicity(%	hepatotoxicity(%
rs11191439	TT	108(77)	67(78)	41(76)
	TC	29(21)	17(20)	12(22)
	CC	3(2)	2(2)	1(2)
	T	245(88)	151(88)	94(87)
	C	35(12)	21(12)	14(13)
rs3740390	CC	112(80)	67((78)	45(83)
	CT	25(18)	16(19)	9(17)
	TT	3(2)	3(3)	0(0)
	C	249(89)	15(87)	99(92)
	T	31(11)	22(13)	9(8)
rs3740393	GG	107(76)	64(74)	43(80)
	GC	28(12)	20(23)	8(15)
	CC	5(4)	2(2)	3(6)
	G	242(86)	148(86)	94(87)
	C	38(14)	24(14)	14(13)

Table 5: Relationship between AS3MT SNPs and hepatotoxicity risk under multiple models of inheritance

SNP ID	Model	Genotype	No Hepatotoxicity (%)	Hepatotoxicity (%)	OR (95% CI)	P	AIC	BIC
rs11191439	Codominant	T/T	67 (77.9%)	41 (75.9%)	1.00			
		T/C	17 (19.8%)	12 (22.2%)	1.24 (0.53-2.90)	0.88	195	209.7
		C/C	2 (2.3%)	1 (1.8%)	1.08 (0.09-13.06)			
	Dominant	T/T	67 (77.9%)	41 (75.9%)	1.00			
		T/C-C/C	19 (22.1%)	13 (24.1%)	1.23 (0.54-2.80)	0.63	193	204.8
	Recessive	T/T-T/C	84 (97.7%)	53 (98.2%)	1.00			
		C/C	2 (2.3%)	1 (1.8%)	1.01 (0.08-12.10)	0.99	193.3	205
	Over dominant	T/T-C/C	69 (80.2%)	42 (77.8%)	1.00			
		T/C	17 (19.8%)	12 (22.2%)	1.24 (0.53-2.88)	0.62	193	204.8
	Log-additive	---	---	---	1.18 (0.57-2.44)	0.66	193.1	204.8
Rs3740390	Codominant	C/C	67 (77.9%)	45 (83.3%)	1.00			
		C/T	16 (18.6%)	9 (16.7%)	0.89 (0.36-2.22)	0.23	192.3	207
		T/T	3 (3.5%)	0 (0%)	0.00 (0.00-NA)			
	Dominant	C/C	67 (77.9%)	45 (83.3%)	1.00			
		C/T-T/T	19 (22.1%)	9 (16.7%)	0.74 (0.30-1.81)	0.51	192.8	204.6
	Recessive	C/C-C/T	83 (96.5%)	54 (100%)	1.00	0.088	190.3	202.1
		T/T	3 (3.5%)	0 (0%)	0.00 (0.00-NA)			
	Over dominant	C/C-T/T	70 (81.4%)	45 (83.3%)	1.00			
		C/T	16 (18.6%)	9 (16.7%)	0.93 (0.37-2.32)	0.87	193.2	205
Rs3740393	Codominant	G/G	64 (74.4%)	43 (79.6%)	1.00			
		G/C	20 (23.3%)	8 (14.8%)	0.62 (0.25-1.53)	0.39	193.4	208.1
		C/C	2 (2.3%)	3 (5.6%)	2.04 (0.32-12.90)			
	Dominant	G/G	64 (74.4%)	43 (79.6%)	1.00			
		G/C-C/C	22 (25.6%)	11 (20.4%)	0.76 (0.33-1.73)	0.5	192.8	204.6
	Recessive	G/G-G/C	84 (97.7%)	51 (94.4%)	1.00			
		C/C	2 (2.3%)	3 (5.6%)	2.23 (0.35-14.00)	0.39	192.5	204.3
	Over dominant	G/G-C/C	66 (76.7%)	46 (85.2%)	1.00			
		G/C	20 (23.3%)	8 (14.8%)	0.60 (0.24-1.48)	0.26	192	203.7
	Log-additive	---	---	---	0.93 (0.48-1.80)	0.82	193.2	205

DISCUSSION

As2O3 has proved its effectiveness in the treatment of APL patients. The occurrence of hepatotoxicity has been well characterized in some APL patients treated with As2O3. Arsenic methyltransferase (AS3MT) is one of the key enzymes involved in the transfer of a methyl group to trivalent arsenical and plays a critical role in arsenic detoxification[19]. Hereditary differences play an important role in interindividual variation. Polymorphisms in the genes involved in metabolism and biotransformation of inorganic arsenic could affect enzyme activity by increasing or decreasing its activation/detoxification.

In this study, we retrospectively investigated the association between three genetic polymorphisms of the AS3MT gene, located in the AS3MT coding and non-coding regions, and hepatotoxicity in 140 APL patients who received As2O3 treatment.

In a recent study by Jing Lu et al., they demonstrated that DMA percentage and SMI were negatively associated with the levels of ALT and AST. Patients with the minor allele (TT and CT) of rs3740390, compared with the rs3740390 CC genotype, had significantly lower levels of ALT and AST[13], denoting that the risk of TT+CT genotype carriers for hepatotoxicity was lower than that of CC gene carriers, a finding not confirmed in our study.

In a more recent study from the same group, compared with APL patients with the rs3740390 CC genotype, those with the TT and TC genotypes had higher DMA and SMI levels and less hepatotoxicity [16]. Moreover, they have shown that the CC genotype is associated with a higher incidence of hyperleukocytosis in patients and have introduced this genotype as a marker that can predict hyperleukocytosis.

However, in another study of 70 APL patients, none of the eighteen polymorphisms, including rs3740390 and rs3740393 had any effect on chronic hepatotoxicity in patients[4].

Although the heterozygous form of SNP rs11191439 showed increased AS3MT enzyme activity, the association of rs11191439 with AS3MT methylation capacity in APL patients needs to be clarified. Limited research has been done on associations of SNPs with hepatotoxicity in APL patients. One of these studies on Asian APL patients has shown that only 4.2% (three out of 70) of patients were heterozygous for SNP M287T.The results of this study demonstrated no significant impact of the rs11191439 genotype on arsenic metabolism [4]. Also, Jing Lu et al., were unable to investigate the association of rs11191439 polymorphism with hepatic toxicity due to the very low allele frequency (only one heterozygous case in 50 APL patients)[13]. In our study, the observed allele frequency of the M287T polymorphism in the AS3MT gene was 12%, which was similar to the frequency observed in European countries but different from East Asian countries, as reported previously[18]. Despite the fact that in our study the allelic frequency of rs11191439 was higher than previous studies on East Asian populations, no association between the rs3740393 polymorphism and hepatotoxicity was found.

Genetic polymorphisms in enzymes involved in arsenic metabolism have been shown to have ethnicity and race-related differences[20-22]. Moreover, genetic variation of other genes involved in arsenic metabolism, such as MTHFR and GST, and non-genetic factors, may contribute to arsenic methylation and distribution in human tissues[3].

The limitation of our study was its retrospective design, and it was not possible to investigate the profile of arsenic metabolites and their association with the AS3MT SNP genotype.

CONCLUSION

In conclusion, this study indicated that three SNPs within AS3MT were not associated with the risk of hepatotoxicity in APL patients treated with As2O3 in our center. To more precisely characterize associations between AS3MT gene polymorphisms and hepatotoxicity, future large-scale studies in non-Asian populations and other ethnicities are needed.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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