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Influence of enzyme and transporter polymorphisms on trough imatinib concentration and clinical response in chronic myeloid leukemia patients

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Background: This study explored the impact of genetic polymorphisms in cytochrome P450 (CYP) enzymes and transporters on the plasma trough concentration of imatinib mesylate (IM) and clinical response in chronic myeloid leukemia (CML).

Patients and methods: In total, 82 patients with CML who had been administered 400 mg IM daily for over 6 months were genotyped for 11 single-nucleotide polymorphisms in nine genes (CYP3A4, CYP3A5, CYP2C9, CYP2C19, CYP2D6, ABCB1, SLC22A1, SLC22A2 and ABCG2) using blood samples. The trough imatinib concentration and clinical responses were assessed 6 months after the initiation of IM therapy.

Results: The CC, CA and AA genotypes in ABCG2 421C>A gave significantly different frequencies for the major molecular response (MMR) ($P = 0.02$). However, no significant differences were found between the genotypes of the CYP enzymes and transporters identified in this study and the imatinib plasma trough concentrations and clinical response frequencies, except for the correlation of ABCG2 with MMR.

Conclusions: The results of the present study may indicate that the ABCG 421C>A genetic polymorphism influences the MMR of imatinib in patients with CML.

Key words: ABCG, chronic myeloid leukemia, clinical response, imatinib trough concentration

introduction

Imatinib mesylate (IM), a selective tyrosine kinase inhibitor, is prescribed to treat chronic myeloid leukemia (CML) and gastrointestinal stromal tumors [1, 2]. IM has dramatically improved the long-term survival rate and clinical response of CML patients, but suboptimal response and response failure to the treatment are also observed [3, 4]. Several mechanisms that lead to IM resistance have been investigated, including the suggestion that pharmacogenetic variability influences the pharmacokinetics of IM [4, 5]. It is well known that IM pharmacokinetics have an obvious correlation with the cytogenetic and molecular responses of CML [6, 7]. It has also

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been suggested that genetic polymorphisms of cytochrome P450 (CYP) enzymes and transporters influence the IM pharmacokinetics leading to IM resistance.

IM is metabolized by the CYP system in the liver, in which the isoenzymes CYP3A4 and CYP3A5 play a major role. Other isoenzymes, including CYP1A2, CYP2D6, CYP2C9 and CYP2C19, are also known to contribute to the metabolism of IM, but to a relatively minor extent [8–12]. IM is a substrate for the breast cancer resistance protein (BCRP) encoded by ABCG2, the p-glycoprotein encoded by ABCB1 and the organic cation transporter 1 encoded by SLC22A1 [13–19].

In this study, we investigated the influence of genetic polymorphisms on the CYP enzymes and transporters linked to the pharmacokinetics of IM using trough imatinib concentration and clinical response in CML patients. We used blood samples to perform genotyping and clinical information from a previous study to evaluate the correlation of trough IM concentration with the cytogenetic or molecular response in Korean CML patients [20].

methods

subjects and study design

This study was carried out according to the declaration of Helsinki and the International Conference on Harmonization-Good Clinical Practice standards. The study protocol was approved by the local institutional review boards, and all volunteers signed written informed consent after receiving a full explanation of the study. In total, 100 patients with newly diagnosed chronic phase CML were enrolled from 23 major hospitals in Korea, and 82 patients were finally enrolled. These comprised 58 male and 24 female patients with a median age of 50 (range 17–79) years. Each patient was orally administered 400 mg IM daily for at least 6 months. The cytogenetic response, measured by bone marrow aspiration, was assessed at diagnosis and after 6 months. The molecular response using peripheral blood was assessed at diagnosis and then every 3 months. A complete cytogenetic response (CCyR) was defined as 0% of Philadelphia chromosome-positive cells based on the full analysis of 20 metaphases of bone marrow. A major molecular response (MMR) was defined as a more than three-log reduction in *BCR-ABL* transcripts compared with the baseline value. CCyR was achieved in 63 patients (76.8%) and MMR in 13 (15.9%) at 6 months after treatment.

laboratory analysis

genotyping

DNA extraction from blood samples was carried out using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Genotyping for the CYP3A4*18 (878T>C), CYP3A5*3C (6986A>G), CYP2C9*3 (1075A>C), CYP2C19*2 (681G>A), CYP2C19*3 (636G>A), CYP2D6*10B (100C>T), ABCB1 1236C>T, ABCB1 3435C>T, SLC22A1 1022C>T, SLC22A2 808G>T and ABCG2 421C>A alleles was carried out using the TaqMan® allelic discrimination assay (Applied Biosystems, Foster City, CA, USA) [21]. The pre-developed TaqMan assay reagent kit (Applied Biosystems) was used, and polymerase chain reaction (PCR) was carried out in 384-well PCR plates using Real-Time PCR 7900H (ABI, USA) as per the standard TaqMan allelic discrimination assay protocol provided by Applied Biosystems. The Hardy–Weinberg equilibrium was confirmed for all of the analyzed single-nucleotide polymorphism (SNP) data.

plasma IM concentration and RQ-PCR

Blood sampling for trough plasma imatinib concentration was carried out between 21 and 27 h after the last IM dosing. Plasma samples were prepared and analyzed using high performance liquid chromatography–mass spectrometry, following a method described previously [22].

The molecular response was assessed as the BCR–ABL/ABL log ratio using real-time quantitative reverse transcriptase PCR (RQ-PCR) in the single laboratory (ISU ABXIS Co., Ltd., Seoul), following a method described previously [23]. Total RNA was extracted from the peripheral blood samples, and the ratio of BCR–ABL fusion transcripts to ABL transcripts was quantified. ABL was used as the control gene. The standardized baseline value was determined as the median value of the BCR–ABL/ABL level of 20 newly diagnosed chronic phase CML patients before IM medication [24].

statistical analysis

Statistical differences of imatinib trough concentration between genotypes of each SNP were determined using Kruskal–Wallis or Mann–Whitney tests. Statistical differences of cytogenetic and molecular responses between genotypes of each SNP were determined using Chi-square or Fisher's exact tests. *P*-values <0.05 were deemed to indicate statistical significance.

results

genotype and imatinib concentration

Genotypes and allele frequencies for all genes evaluated in this study are shown in Table 1. The Hardy–Weinberg equilibrium test was confirmed for all genotypes.

The comparisons of imatinib trough concentration with enzyme and transporter genotypes are shown in Table 2. There were no statistically significant differences in the imatinib trough concentration when comparing all enzyme and transporter genotypes.

genotype and clinical response

A comparison of the cytogenetic response among enzyme and transporter genotypes is summarized in Table 3. The

Table 1. Genotype and allele frequencies of the genes evaluated in this study

Variant	Genotype frequency			Allele frequency	
	Wild	Hetero	Variant	*P*	*q*
Enzyme genotype					
CYP3A4*18 (878T>C)	77 (93.9)	5 (6.1)	0 (0)	0.970	0.030
CYP3A5*3C (6986A>G)	3 (3.7)	27 (32.9)	52 (63.4)	0.201	0.799
CYP2C9*3 (1075A>C)	77 (93.9)	5 (6.1)	0 (0)	0.970	0.030
CYP2C19*2 (681G>A)	42 (51.2)	37 (45.1)	3 (3.7)	0.738	0.262
CYP2C19*3 (636G>A)	65 (79.3)	17 (20.7)	0 (0)	0.896	0.104
CYP2D6*10B (100C>T)	24 (29.3)	35 (42.7)	23 (28.0)	0.506	0.494
Transporter genotype					
ABCB1 1236C>T	17 (20.7)	37 (45.1)	28 (34.1)	0.433	0.567
ABCB1 3435C>T	35 (42.7)	38 (46.3)	9 (11.0)	0.659	0.341
SLC22A1 1022C>T	58 (70.7)	24 (29.3)	0 (0)	0.854	0.146
SLC22A2 808G>T	67 (81.7)	15 (18.3)	0 (0)	0.909	0.091
ABCG2 421C>A	41 (50.6)	32 (39.5)	8 (9.9)	0.704	0.296

Table 2. Comparison of imatinib trough concentration with the enzyme and transporter genotypes

Genotype	*n*	Imatinib trough concentration (ng/ml)		*P*-value
		Mean	SD	
Enzyme genotype				
CYP3A4*18 (878T>C)				
Wild	77	1348.8	715.6	0.71
Hetero	5	1330.4	339.3	
CYP3A5*3C (6986A>G)				
Wild	3	1366.7	526.9	0.50
Hetero	27	1386.8	538.6	
Variant	52	1326.3	782.4	
CYP2C9*3 (1075A>C)				
Wild	77	1349.2	705.7	0.86
Hetero	5	1324.6	617.7	
CYP2C19*2 (681G>A)				
Wild	42	1428.4	602.7	0.18
Hetero	37	1265.2	809.6	
Variant	3	1235.3	407.2	
CYP2C19*3 (636G>A)				
Wild	65	1315.6	692.2	0.41
Hetero	17	1470.5	724.4	
CYP2D6*10B (100C>T)				
Wild	24	1501.6	908.6	0.15
Hetero	35	1381.0	583.2	
Variant	23	1136.4	572.0	
Transporter genotype				
ABCB1 1236C>T				
Wild	17	1326.9	479.4	0.57
Hetero	37	1282.3	617.2	
Variant	28	1446.7	893.4	
ABCB1 3435C>T				
Wild	35	1211.1	469.3	0.62
Hetero	38	1455.3	844.0	
Variant	9	1424.7	741.0	
ABCB1 haplotype				
C–C	71	1303.6	65.2	0.52
C–T	37	1284.2	127.6	
T–T	56	1445.4	106.8	
SLC22A1 1022C>T				
Wild	58	1374.0	606.8	0.23
Hetero	24	1284.0	890.9	
SLC22A2 808G>T				
Wild	67	1396.2	735.9	0.23
Hetero	15	1131.2	445.4	
ABCG2 421C>A				
Wild	41	1227.5	582.3	0.15
Hetero	32	1459.8	864.3	
Variant	8	1563.4	404.1	

Table 3. Comparison of cytogenetic response with the enzyme and transporter genotypes

Genotype	*n*	CCyR	Non-CCyR	*P*-value
Enzyme genotype				
CYP3A4*18 (878T>C)				
Wild	77	59	18	1.00
Hetero	5	4	1	
CYP3A5*3C (6986A>G)				
Wild	3	2	1	0.64
Hetero	27	22	5	
Variant	52	39	13	
CYP2C9*3 (1075A>C)				
Wild	77	59	18	1.00
Hetero	5	4	1	
CYP2C19*2 (681G>A)				
Wild	42	30	12	0.34
Hetero	37	31	6	
Variant	3	2	1	
CYP2C19*3 (636G>A)				
Wild	65	48	17	0.21
Hetero	17	15	2	
CYP2D6*10B (100C>T)				
Wild	24	20	4	0.10
Hetero	35	29	6	
Variant	23	14	9	
Transporter genotype				
ABCB1 1236C>T				
Wild	17	15	2	0.13
Hetero	37	30	7	
Variant	28	18	10	
ABCB1 3435C>T				
Wild	35	30	5	0.13
Hetero	38	28	10	
Variant	9	5	4	
ABCB1 haplotype				
C–C	71	60	11	0.09
C–T	37	28	9	
T–T	56	38	18	
SLC22A1 1022C>T				
Wild	58	43	15	0.37
Hetero	24	20	4	
SLC22A2 808G>T				
Wild	67	51	16	1.00
Hetero	15	12	3	
ABCG2 421C>A				
Wild	41	34	7	0.52
Hetero	32	23	9	
Variant	8	6	2	

frequencies of CCyR and non-CCyR were compared between genotypes using Chi-square or Fisher's exact tests. There were no statistically significant differences in cytogenetic response frequency for any enzyme or transporter genotype investigated in this study.

A comparison of the molecular response among enzyme and transporter genotypes is summarized in Table 4. The frequencies of MMR and non-MMR were compared between the genotypes using Chi-square or Fisher's exact tests. There were no statistically significant differences in the molecular response among any of the enzyme or transporter genotypes investigated in this study, except for ABCG2 421C>A.

In ABCG2 421C>A, the frequency of MMR was 5 of 41 patients with the CC genotype, 4 of 32 with the CA genotype

Table 4. Comparison of molecular response with the enzyme and transporter genotypes

Genotype	*n*	MMR	Non-MMR	*P*-value
Enzyme genotype				
CYP3A4*18 (878T>C)				
Wild	77	11	66	0.18
Hetero	5	2	3	
CYP3A5*3C (6986A>G)				
Wild	3	1	2	0.25
Hetero	27	6	21	
Variant	52	6	46	
CYP2C9*3 (1075A>C)				
Wild	77	12	65	1.00
Hetero	5	1	4	
CYP2C19*2 (681G>A)				
Wild	42	8	34	0.74
Hetero	37	5	32	
Variant	3	0	3	
CYP2C19*3 (636G>A)				
Wild	65	10	55	1.00
Hetero	17	3	14	
CYP2D6*10B (100C>T)				
Wild	24	6	18	0.40
Hetero	35	4	31	
Variant	23	3	20	
Transporter genotype				
ABCB1 1236C>T				
Wild	17	3	14	0.46
Hetero	37	4	33	
Variant	28	6	22	
ABCB1 3435C>T				
Wild	35	6	29	0.38
Hetero	38	7	31	
Variant	9	0	9	
ABCB1 haplotype				
C–C	71	10	61	0.27
C–T	37	9	28	
T–T	56	7	49	
SLC22A1 1022C>T				
Wild	58	8	50	0.51
Hetero	24	5	19	
SLC22A2 808G>T				
Wild	67	10	57	0.70
Hetero	15	3	12	
ABCG2 421C>A				
Wild (CC)	41	5	36	0.02
Hetero (CA)	32	4	28	
Variant (AA)	8	4	4	
Wild + hetero	73	9	64	0.02
Variant	8	4	4	
Wild	41	5	36	0.34
Hetero + variant	40	8	32	

and 4 of 8 with the AA genotype ($P = 0.02$). The comparison of CC + CA with AA genotypes was also significantly different ($P = 0.02$). The odds ratio of CC + CA over AA was 0.14 (95% confidence interval 0.03–0.66).

discussion

ABCG2 421C>A in exon 5 is a non-synonymous SNP, where a glutamine is substituted with a lysine residue at codon 141 (Q141K). Our data suggest that the ABCG2 421 variant allele is related to a higher rate of MMR in CML patients using imatinib. Although there was no statistically significant difference in trough imatinib concentrations between the ABCG2 421C>A genetic variants, the mean value was higher in the group with more A variants. The mean trough imatinib concentrations of the CC, CA and AA groups were 1227.5 ± 582.3, 1459.8 ± 864.3 and 1563.4 ± 404.1 ng/ml (mean ± standard deviation [SD]), respectively ($P = 0.15$).

It has been reported that human embryonic kidney 293 cells transfected with ABCG2 Q141K showed a higher imatinib accumulation compared with wild-type ABCG2 *in vitro* [14]. In a further study, it was determined that dose-adjusted imatinib trough concentrations were higher in patients with the CA or AA genotype compared with the CC genotype in 67 Japanese CML patients [15]. In the same study, there was no significant correlation observed between clinical responses and ABCG2 421 genetic variants [15]. However, the clinical relevance of ABCG2 421C>A with imatinib was demonstrated in a study of 229 Canadian CML patients [25]. In this study, the AA genotype exhibited a higher MMR than the CA or CC genotype.

The influence of ABCG2 421C>A on imatinib concentration and clinical response is good agreement with this and other previous reports, although some studies failed to determine the effect of ABCG2 421C>A on the imatinib response.

Oral absorption of imatinib is rapid and almost complete; the absolute bioavailability is >97% [26]. Imatinib is extensively metabolized after absorption and excreted mainly through the biliary route. The recovery of the administered dose in feces is >70%, detected as imatinib or its metabolites [27]. In the process of excretion, BCRP encoded by ABCG2 at the apical membrane of hepatocytes may play a substantial role. Therefore, the genetic variability of the ABCG2 gene may influence the variability of the pharmacokinetics and clinical response of imatinib.

In conclusion, this study showed that ABCG2 421C>A genetic variation may influence the molecular response of imatinib in CML patients. Although further studies are needed to confirm this result due to the non-confirmative ABCG2 421C>A data and the complexity of other influencing factors, ABCG2 421C>A genotyping may be used to predict the clinical response and applied to the refinement of the imatinib dose in CML patients.

disclosure

The authors have declared no conflicts of interest.

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