Effects of Trough Concentration and Solute Carrier Polymorphisms on Imatinib Efficacy in Chinese Patients with Chronic Myeloid Leukemia

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ABSTRACT-Purpose: We investigated the relationship between imatinib trough concentrations and genetic polymorphisms with efficacy of imatinib in Chinese patients with chronic myeloid leukemia (CML). Methods: There were 171 eligible patients. Peripheral blood samples were collected from 171 eligible patients between 21 and 27 hours after the last imatinib administration. Complete cytogenetic response (CCyR), major molecular response (MMR) and complete molecular response (CMR) were used as metrics for efficacy. Nine single nucleotide polymorphisms in 5 genes, SLC22A4 (-361 G>A), SLC22A5 (-945 T>G and -1889 T>C), SLCO1A2 (-361 G>A), SLCO1B3 (-334 T>G and -699 G>A) and ABCG2 (421C>A) were selected for genotyping. Results: Patients with CCyR achieve higher trough concentrations than those without CCyR (1478.18±659.83 vs 984.89±454.06 ng mL\textsuperscript{-1}, p<0.001). Patients with MMR and CMR achieve higher trough concentrations than those without MMR and CMR, respectively (1486.40±703.38 vs 1121.17±527.14 ng mL\textsuperscript{-1}, p=0.007; 1528.00±709.98 vs 1112.67±518.35 ng mL\textsuperscript{-1}, p=0.003, respectively). Carriers of A allele in SLCO1A2 -361G>A achieve higher CCyR and MMR rates (p=0.047, OR=4.320, 95% CI: 1.016-7.853, respectively). Both trough concentrations and SLCO1A2 -361G>A genotypes are independent factors affecting imatinib efficacy. The positive and negative predictive values for CCyR are 71.01% and 68.75%, respectively. The positive and negative predictive values for MMR are 62.86% and 69.70%, respectively. Conclusion: Imatinib trough concentrations and SLCO1A2 -361G>A genotypes are associated with imatinib efficacy in Chinese patients with CML. Keywords: Efficacy, Imatinib, Polymorphisms, Trough concentration

INTRODUCTION

Imatinib mesylate is a potent and competitive inhibitor of the BCR-ABL tyrosine kinase and is the drug of choice for chronic myeloid leukemia (CML) (1). Imatinib has dramatically improved the quality of life and long-term survival rate of patients with CML (2). However, many patients still experienced suboptimal response and treatment failure. The reason for this is unclear. One theory is that point mutations in the ATP binding site and amplification of BCR-ABL gene could contribute to imatinib resistance (3). This could be one explanation for the observed treatment failure. A previous meta-analysis found more than sevenfold inter-patient variability in imatinib trough concentrations (ranged from 420-3253 ng mL\textsuperscript{-1}) (4). Large inter-patient variability in imatinib pharmacokinetics was also an important cause of unpredictable clinical response between patients (5, 6). Complete molecular response (CMR) is an important metric for optimal response, therefore, patients with persistent CMR could discontinue imatinib therapy (7). Nevertheless, limited studies about the association of imatinib trough concentrations with CMR have shown inconsistent results (8, 9).
The meta-analysis found a significant association of plasma imatinib trough concentrations with complete cytogenetic response (CCyR) and major molecular response (MMR) in Asian patients with CML, but no significant association between the trough concentrations and CMR (4). Since the meta-analysis do not include data from Chinese patients with CML, further prospective studies to identify the relationship between imatinib trough concentrations and CCyR, MMR and especially CMR in Chinese patients with CML are still required.

Genetic polymorphisms of transporters could play an important role in imatinib disposition and clinical response (10). Imatinib is a substrate for solute carrier transporters (SLCs), such as organic cation/carnitine transporter 1 (OCTN1, encoded by SLC22A4), organic cation/carnitine transporter 2 (OCTN2, encoded by SLC22A5), organic anion-transporting polypeptide 1A2 (OATP1A2, encoded by SLCO1A2), organic anion-transporting polypeptide IB3 (OATP1B3, encoded by SLCO1B3), and a substrate for efflux transporters such as P-glycoprotein (P-gp, encoded by ABCB1) and breast cancer resistance protein (BCRP, encoded by ABCG2) (11, 12). These transporters exist in multiple tissues including the intestine, liver and bone marrow, which contribute to imatinib intestinal absorption, hepatic and target cells intake, respectively (10, 13). Genetic polymorphisms of the candidate genes SLC22A4, SLC22A5, SLCO1A2, SLCO1B3, ABCB1 and ABCG2, which contribute to altered expression and/or activity of corresponding transporters, may be key determinants to variable pharmacokinetics and clinical response in individuals (10). Previously, limited studies about SLC22A4, SLC22A5, SLCO1A2 and SLCO1B3 genes mutation effects on imatinib pharmacokinetics and/or efficacy showed inconsistent results and were mainly conducted in Caucasian patients with CML (14-16). Two previous studies conducted in Japanese patients with CML only investigated the effects of SLCO1A2 and SLCO1B3 polymorphisms on imatinib pharmacokinetics (17, 18). These two studies did not analyze the relationship between these two genes polymorphisms and clinical response. Thus, prospective studies to clarify the relationship between these four genes polymorphisms and efficacy of imatinib in Chinese patients with CML are necessary. Moreover, there are some studies investigating the relationship between ABCB1 and ABCG2 polymorphisms and imatinib clinical response, with inconsistent results.

A previous meta-analysis found no significant association between ABCB1 polymorphisms and imatinib clinical response (4). Also, the meta-analysis found no significant association between ABCG2 polymorphisms and CCyR rate, but a significant association of ABCG2 polymorphisms with MMR rate in patients with CML (4). Since the meta-analysis do not include data from Chinese patients with CML, further prospective studies to identify the relationship between ABCG2 polymorphisms and efficacy of imatinib in Chinese patients with CML are still required.

Considering these aspects, the objectives of this study are to i) analyze the relationship between imatinib trough concentrations and efficacy especially CMR, and ii) investigate the effects of SLC22A4, SLC22A5, SLCO1B3, SLCO1A2 and ABCG2 polymorphisms on imatinib efficacy in Chinese patients with CML.

METHODS

Patients

The study was performed in accordance with the Declaration of Helsinki and was approved by the Second Xiangya Hospital of Central South University Ethics Committee (XY2-PK-TKI-2016A01). Informed consent was obtained from all participants. The clinical trial registration number is ChiCTR-RPC-16010078. The study was conducted in Xiangya Hospital of Central South University and the Second Xiangya Hospital of Central South University between June 2016 and July 2017. All patients initially received imatinib 400 mg once a day orally. Dose reduction was allowed for patients with severe adverse events (recurrence of absolute neutrophil count (ANC) <1.0×10^9/L and/or platelets 50×10^9/L), and dose increase was allowed for patients with suboptimal response (after imatinib treatment for 1 year, BCR-ABL transcripts: 1-10%).

The exclusion criterions were: 1) patients received concomitant medications known to affect imatinib pharmacokinetics such as ketoconazole; 2) patients with concomitant cancers; 3) patients lack routine laboratory tests such as complete blood cell counts and genetic testing for BCR-ABL fusion gene. Patients were followed up in the clinic every 3 months until CCyR is obtained and maintained for 2 years. After that the patients will be follow up every 3 - 6 months for life.

Sample collection and measurement of plasma imatinib concentrations

The steady-state plasma trough concentration after at
least one month of therapy was used to represent exposure of imatinib (19). Peripheral blood samples were collected from eligible patients between 21 and 27 hours after the last imatinib administration for plasma trough concentrations. Imatinib plasma concentrations was determined using ultra performance liquid chromatography-mass spectrometry (UPLC-MS/MS) (Waters, USA), following the reported method previously (20). The internal standard was gliquidone. The linearity range was 2.60-5250.00 ng/ml. The intra-day and inter-day precisions were within 1.51%-12.30% and 4.46%-13.26%, respectively. For the low concentrations, the intra-day and inter-day precisions were 7.87% and 13.26%, respectively.

Evaluating imatinib efficacy
In this study, CCyR, MMR and CMR were metrics for efficacy. Only patients received imatinib therapy continuously for more than 6 months were available for efficacy assessment. Cytogenetic and molecular response was evaluated according to National Comprehensive Cancer Network (NCCN) guidelines (21). CCyR is defined as no Ph-positive metaphases in minimum 20 examined cells by bone marrow aspirate or \textit{BCR-ABL} transcripts \(\leq 1\%\) IS. MMR and CMR are defined as \textit{BCR-ABL} transcripts \(\leq 0.1\%\) IS and \textit{BCR-ABL} transcripts \(\leq 0.0032\%\) IS respectively.

Genotyping
Total genomic DNA extraction from the blood samples for genotyping was carried out by phenol–chloroform method. The purity and concentration of DNA samples were analyzed by an Eppendorf Biospectrometer (Eppendorf, Germany). Nine single nucleotide polymorphisms (SNPs) in 5 genes, \textit{SLC22A4} (917 T>C, -248 C>G and -538 C>G), \textit{SLC22A5} (-945 T>G and -1889 T>C), \textit{SLCO1A2} (-361 G>A), \textit{SLCO1B3} (334 T>G and 699 G>A) and \textit{ABCG2} (421C>A) were selected for genotyping, so as to investigate the effects of these genetic polymorphisms on imatinib trough concentrations, efficacy. All SNPs were determined by using polymerase chain reaction (PCR) and then Sanger sequencing. Analyses were carried out using an Applied Biosystems® SimpliAmp™ Thermal Cycler (Thermo Fisher Scientific, New York, USA). Sequencings were performed on Applied Biosystems 3730XL DNA Analyzer (Applied Biosystems, Forster, CA, USA). The genotyping accuracy was confirmed by duplicates of all samples. All forward and reverse primers were self-designed for 917 T>C (F: 5’ TATGGTCTGTCCTGGGTTCG-3’ and R: 5’ CTGTGCAGGTGTGTTTG GAGC-3’), -248 C>G and -538 C>G (F: 5’-AACCGACTCCACTGACTCG-3’ and R: 5’-GGCTGTTAGAAATTGGGGGC-3’), -945 T>G (F: 5’-AGCAATGGCCCAATAAAATACAGG-3’ and R: 5’-CAGCGAGGTGATTCATCAAAGCA-3’), -1889 T>C (F: 5’-TCATCTTGGTTGGTCTGGACACG-3’ and R: 5’-GACAGCACCTCCTCATA GGC-3’), -361 G>A (F: 5’-TAGGGAAGCCTTGGGAATGC-3’ and R: 5’-ACCTGGAAGGGTTGGAATAGA-3’), 334 T>G and 699 G>A (F: 5’-TGTCAGGATGTCCTCAGAC-3’ and R: 5’-GCAGCAGCTGAAGTTGTA AA-3’), 917 T>C, -248 C>G and -538 C>G (F: 5’-TGTCAGGATGTCCTCAGAC-3’ and R: 5’-TGTCAGGATGTCCTCAGAC-3’), 917 T>C, -248 C>G and -538 C>G (F: 5’-TGTCAGGATGTCCTCAGAC-3’ and R: 5’-TGTCAGGATGTCCTCAGAC-3’).

PCR reactions were performed in a 25-microliter mixture with 0.4μM (micromoles per liter) of each primer, 2× Taq plus Master Mix (Dye plus) (Vazyme, Nanjing, China), genomic DNA templates and ddH₂O. The amplification program was 95℃/3min for initial denaturation, followed by 30 cycles of 95℃/30s for denaturation, 53℃ (-945 T>G) /55℃ (-1889 T>C, -361 G>A, 699 G>A and 421C>A) /57℃ (917 T>C, -248 C>G and -538 C>G) /58℃ (334 T>G) /30s for annealing and 72℃/ 1min for extension. The ending extension was performed at 72℃ for 5minutes.

Data presentation and statistical analysis
All analyses were performed by SPSS statistical software (version 17.0, IBM., USA). The Hardy-Weinberg equilibrium was tested for all analyzed genotype frequencies. All figures were acquired using GraphPad Prism 6 software (GraphPad Software, Inc., USA) and OriginPro 9 software (OriginLab, Inc., USA). All continuous data were expressed as mean values and standard deviations (mean \(\pm\) SD), and categorical data were expressed as frequencies and percentages. Mann-Whitney test was used to analyze the relationship between trough concentrations and efficacy. Kruskal-Wallis test was used to determine the relationship between imatinib trough concentrations and genotypes of each SNP. Chi-square or Fisher’s exact tests were used to analyze the differences of efficacy among patients with various genotypes. Backward stepwise logistic regression analysis for efficacy was conducted to determine the independent effect of variables evaluated in univariate analysis (\(\alpha_{\text{inclusion}} = 0.10\), and
\[ \alpha_{\text{elimination}} = 0.15 \]. Variables with \( p \)-value less than 0.10 in Mann-Whitney test, Chi-square or Fisher’s exact tests were included in logistic regression analysis. \( p \leq 0.05 \) were considered statistically significant.

**RESULTS**

**Patient characteristics and genotype frequencies**

A total of 173 patients with CML are eligible for the study but only 171 patients are included (170 with chronic phase and 1 with accelerated phase). Two patients are excluded for missing laboratory data in the medical record. Demographics of participants are shown in Table 1. A total of 116 patients receive imatinib 400 mg once daily. The efficacy of study patients is evaluated on the same day as samples are collected and analyzed. The flow chart shows the details of the patient numbers for trough concentrations and efficacy assessments (Figure. 1).

The frequencies of selected genotypes in all participants (171) are in accordance with Hardy-Weinberg equilibrium (HWE) (Table S1).

**Relationship between imatinib trough concentrations and efficacy**

Trough concentrations were measured for 109 patients because not all samples were obtained at the correct sampling time. However, only 101 patients are included in the analysis of the relationship between trough concentrations and efficacy because 8 patients who have been measured the trough concentrations receive imatinib therapy continuously for less than 6 months and are not available for CCyR, MMR and CMR assessment. Patients with CCyR, MMR and CMR achieve significantly higher trough concentrations than those without these corresponding efficacy (1478.18±659.83 vs 984.89 ± 454.06 ng mL\(^{-1}\), \( p<0.001 \); 1486.40 ± 703.38 vs 1121.17 ± 527.14 ng mL\(^{-1}\), \( p=0.007 \); 1528.00 ± 709.98 vs 1112.67 ± 518.35 ng mL\(^{-1}\), \( p=0.003 \), respectively) (Figure. 2).

**Effects of transporter polymorphisms on imatinib trough concentrations**

There are 109 imatinib trough concentrations. Among them, only 72 patients receive imatinib 400 mg once daily and their trough concentrations are used to analyze the relationship between transporter genotypes and imatinib trough concentrations. In all 9 SNPs, there are no statistically significant relationship between imatinib trough concentrations and each \( SLC22A4 \), \( SLC22A5 \), \( SLCO1A2 \), \( SLCO1B3 \) and \( ABCG2 \) genotype (Table 2).

| Characteristics                        | mean±SD /median (range) | n     |
|----------------------------------------|-------------------------|-------|
| Age (years)                            | 43.61±12.27 (16-82)     | 170/1 |
| Height (m)                             | 1.64±0.08 (1.45-1.8)    |       |
| Weight (kg)                            | 61.81±11.26 (42.5-101)  |       |
| BMI (kg m\(^{-2}\))                    | 23.05±3.35 (15.06-34.64)| 97/74 |
| Sex (male/female)                      |                         |       |
| Stage of disease (chronic/accelerated phase) | 170/1                  |       |
| Duration of treatment (months)         | 15.5 (0.03-170.37)      |       |
| Dosage (100/200/300/400/600 mg)        | 2/11/40/116/2           |       |
| CCyR (yes/no)                          | 109/40                  |       |
| MMR (yes/no)                           | 79/70                   |       |
| CMR (yes/no)                           | 62/87                   |       |

Abbreviations: CML= chronic myeloid leukemia; \( SD \)=standard deviation; BMI=Body Mass Index; CCyR=complete cytogenetic response; MMR= major molecular response; CMR=complete molecular response
A total of 173 patients with CML were eligible for the study
Excluding: patients with missing laboratory data in the medical records (n=2)
A total of 171 patients with CML were included
Excluding: patients in accelerated phase (n=1)
Efficacy assessment in chronic phase patients (n=170)
Excluding: patients with incorrect sampling time (n=61); Patients receiving imatinib therapy continuously for less than 6 months (n=8)
Relationship between imatinib trough concentrations and efficacy (n=101)
Excluding: patients receiving imatinib therapy continuously for less than 6 months (n=21); patients with non-standard dosage (400 mg once daily) (n=54)
Effects of transporter polymorphisms on imatinib efficacy (n=95)
Excluding: patients with incorrect sampling time (n=62); patients with non-standard dosage (400 mg once daily) (n=37)
Effects of transporter polymorphisms on imatinib trough concentrations (n=72)
Excluding: patients with incorrect sampling time (n=62); patients with non-standard dosage (400 mg once daily) (n=37)

Figure 1. The flow chart showing the details of the patient numbers for trough concentrations and efficacy assessments. Abbreviation: CML, chronic myeloid leukemia.

Figure 2. Box-scatter plots of imatinib trough concentrations in patients with and without CCyR (a), in patients with and without MMR (b) and in patients with and without CMR (c). Abbreviations: CCyR, complete cytogenetic response; MMR, major molecular response; CMR, complete molecular response.
Table 2. Association between transporter genotypes and imatinib trough concentrations

| genotypes          | n   | mean±SD            | p       |
|--------------------|-----|--------------------|---------|
| SLC22A4 917T>C     |     |                    |         |
| T/T                | 34  | 1571.96±761.24     | 0.307   |
| T/C                | 32  | 1299.78±665.42     |         |
| C/C                | 6   | 1315.07±703.16     |         |
| SLC22A4 -538C>G    |     |                    |         |
| C/C                | 14  | 1588.91±901.99     | 0.759   |
| C/G                | 28  | 1459.75±734.65     |         |
| G/G                | 30  | 1327.08±609.80     |         |
| SLC22A4 -248C>G    |     |                    |         |
| C/C                | 14  | 1588.91±901.99     | 0.759   |
| C/G                | 28  | 1459.75±734.65     |         |
| G/G                | 30  | 1327.08±609.80     |         |
| SLC22A5 -1889T>C   |     |                    |         |
| T/T                | 6   | 1315.07±703.16     | 0.444   |
| T/C                | 32  | 1312.21±654.95     |         |
| C/C                | 34  | 1560.26±773.78     |         |
| SLC22A5 -945T>G    |     |                    |         |
| T/T                | 35  | 1387.26±780.63     | 0.547   |
| T/G                | 30  | 1520.94±695.17     |         |
| G/G                | 7   | 1249.68±475.21     |         |
| SLC21B 334T>G      |     |                    |         |
| T/T                | 6   | 1493.81±800.27     | 0.382   |
| T/G                | 27  | 1416.42±608.43     |         |
| G/G                | 39  | 1071.36±588.49     |         |
| SLC21B3 699G>A     |     |                    |         |
| G/G                | 6   | 1493.81±800.27     | 0.382   |
| G/A                | 27  | 1416.42±608.43     |         |
| A/A                | 39  | 1071.36±588.49     |         |
| ABCG2 421C>A       |     |                    |         |
| C/C                | 38  | 1532.78±755.26     | 0.358   |
| C/A                | 31  | 1266.72±573.49     |         |
| A/A                | 3   | 1112.39 ±         |         |

Abbreviations: *a*, median. SD=standard deviation; Quantitative variables were compared using the Kruskal-Wallis test.

Effects of transporter polymorphisms on imatinib efficacy

Only 149 patients with chronic phase are available for CCyR, MMR and CMR assessment because 21 patients receive imatinib therapy continuously for less than 6 months. About 73.2% (109/149) achieve CCyR, 53.05 % (79/149) achieve MMR and 41.6 % (62/149) achieve CMR. Only 95 patients receive imatinib 400mg once a day and their efficacy metrics are used to analyze the relationship between transporter genotypes and imatinib efficacy. Comparisons of CCyR and MMR among transporter genotypes are shown in table 3.

The results show no statistically significant relationship between CCyR or MMR and 8 genotypes. Only SLC01A2 -361G>A genotypes significantly affect CCyR or MMR. There are 24 patients with G/A genotype and 5 patients with A/A genotype in this study population. Of these 29 patients with mutate allele A, 27 patients achieve CCyR and 23 patients achieve MMR. There are 66 patients with G/G genotype and 50 of these patients achieve CCyR, and 38 of these patients achieve MMR. There is a statistically significant difference in CCyR rate achieved by G/A or A/A genotypes compared with G/G genotype (93.1% vs 75.8%,
The odds ratio (OR) of genotypes with mutate allele A (G/A or A/A) over G/G genotype is 4.320 (95% Confidence interval (CI): 0.924-20.206). Also, there is a statistically significant difference in MMR rate achieved by G/A or A/A genotypes compared with G/G genotype (79.3% vs 57.6%, \( p=0.042 \)) (Figure. S1b). The OR of genotypes with mutate allele A (G/A or A/A) over G/G genotype is 2.825 (95%CI: 1.016-7.853). There is no statistically significant relationship between CMR rate and genotypes of all transporters (Table S2).

### Table 3. Association between genotypes and imatinib cytogenetic and molecular response

| genotypes       | n | CCyR | Non-CCyR | p  | MMR | Non-MMR | p     |
|-----------------|---|------|----------|----|-----|---------|-------|
| SLC22A4 917T>C  |   |      |          |    |     |         |       |
| T/T             | 41| 33   | 8        | 0.884 | 25 | 16 | 0.769 |
| T/C             | 41| 34   | 7        | 0.884 | 28 | 13 |       |
| C/C             | 13| 10   | 3        | 0.884 | 8  | 5  |       |
| SLC22A4 -538C>G |   |      |          |    |     |         |       |
| C/C             | 18| 14   | 4        | 0.805 | 11 | 7  | 0.518 |
| C/G             | 39| 31   | 8        | 0.805 | 23 | 16 |       |
| G/G             | 38| 32   | 6        | 0.805 | 27 | 11 |       |
| SLC22A4 -248C>G |   |      |          |    |     |         |       |
| C/C             | 18| 14   | 4        | 0.805 | 11 | 7  | 0.518 |
| C/G             | 39| 31   | 8        | 0.805 | 23 | 16 |       |
| G/G             | 38| 32   | 6        | 0.805 | 27 | 11 |       |
| SLC22A5 -361G>A |   |      |          |    |     |         |       |
| G/G             | 66| 50   | 16       | 0.047* | 38 | 28 | 0.042* |
| G/A+A/A         | 29| 27   | 2        | 0.047* | 23 | 6  |       |
| SLC22A5 -1889T>C|   |      |          |    |     |         |       |
| T/T             | 13| 10   | 3        | 0.749 | 8  | 5  | 0.694 |
| T/C             | 39| 33   | 6        | 0.749 | 27 | 12 |       |
| C/C             | 43| 34   | 9        | 0.749 | 26 | 17 |       |
| SLC22A5 -945T>G |   |      |          |    |     |         |       |
| T/T             | 54| 42   | 12       | 0.350 | 33 | 21 | 0.470 |
| T/G+G/G        | 41| 35   | 6        | 0.350 | 28 | 13 |       |
| SLC21B3 334T>G  |   |      |          |    |     |         |       |
| T/T+TG         | 45| 37   | 8        | 0.783 | 29 | 16 | 0.964 |
| G/G             | 50| 40   | 10       | 0.783 | 32 | 18 |       |
| SLC21B3 699G>A  |   |      |          |    |     |         |       |
| G/G+G/A        | 44| 36   | 8        | 0.860 | 28 | 16 | 0.914 |
| A/A             | 51| 41   | 10       | 0.860 | 33 | 18 |       |
| ABCG2 421C>A   |   |      |          |    |     |         |       |
| C/C             | 53| 43   | 10       | 0.982 | 34 | 19 | 0.989 |
| C/A+A/A        | 42| 34   | 8        | 0.982 | 27 | 15 |       |

Abbreviations: CCyR=complete cytogenetic response; non-CCyR=not achievement of complete cytogenetic response; MMR=major molecular response; non-MMR=not achievement of major molecular response. Categorical variables were compared by Chi-square tests. *\( p<0.05 \).

**Backward stepwise logistic regression analysis for efficacy**

The univariate analysis indicates that both trough concentrations and \( SLCO1A2 -361G>A \) genotypes are associated with imatinib efficacy (CCyR and MMR). To determine the independent effect of these two variables, backward stepwise logistic regression analysis is conducted. According to previous studies, patients were divided into two groups with concentrations equal to or greater than 1000 ng mL\(^{-1}\) and less than 1000 ng mL\(^{-1}\) (4)(6). The multivariate analysis indicates that patients with trough concentrations equal to or more than 1000 ng mL\(^{-1}\) (OR: 3.961, 95% CI: 1.676-9.363, \( p=0.002 \)) and A allele in \( SLCO1A2 -361G>A \) (OR: 2.428, 95% CI: 0.955-6.172, \( p=0.062 \)) are more likely to achieve CCyR. The positive and negative predictive values for CCyR are 71.01% and 68.75%, respectively. The multivariate analysis also indicates that patients with trough concentrations equal to or more than 1000 ng mL\(^{-1}\) and less than 1000 ng mL\(^{-1}\) (4)(6) are more likely to achieve MMR (OR: 2.825, 95% CI: 1.016-7.853, \( p=0.062 \)).
mL\(^{-1}\) (OR: 1.938, 95% CI: 1.057-4.550, \(p=0.129\)) and A allele in SLCO1A2 -361G>A (OR: 3.809, 95% CI: 1.576-9.206, \(p=0.003\)) are more likely to achieve MMR. The positive and negative predictive values for MMR are 62.86% and 69.70%, respectively.

DISCUSSION

This is the first study to show a significant relationship between imatinib trough concentrations and CMR in Chinese patients with CML (\(p=0.003\)). This is consistent with one recent study conducted in Caucasian patients (9). Also, this study confirms the significant association of imatinib trough concentrations with CCyR and MMR in Chinese patients with CML, and it is consistent with previous studies conducted in non-Chinese population (4, 9, 22, 23). Therefore, imatinib trough concentrations may be useful to predict efficacy.

Another main finding is the significant effect of SLCO1A2 -361G>A polymorphisms on the CCyR and MMR. The mutant allele in SLCO1A2 -361 G>A is correlated to a higher rate of CCyR and MMR, which indicates that the mutant allele has a favorable impact to achieve CCyR and MMR. The results show no significant relationship between CMR and the genotypes in this study, which might be attributed to less patients achieving CMR and a low frequency of some certain genotypes, resulting in low significant power. However, the relationship between SLCO1A2 -361G>A genotypes and imatinib efficacy was not found in a study with 118 Brazil patients with CML (16). These inconclusive results may be partially attributed to studies with limited sample sizes, heterogeneity of study population and different clinical endpoints. Interestingly, SLCO1A2 -361G>A genotypes are associated with imatinib efficacy but not with imatinib trough concentrations in this study (Figure. S2). Due to the deficiency of functional study on SNPs in the promoter region of SLCO1A2, the mechanism behind the effect of SLCO1A2 -361G>A polymorphisms on the efficacy of imatinib requires further investigation.

This study fails to find a significant relationship between imatinib trough concentrations and any of the transporter genotypes investigated in this study population, which was consistent with one population pharmacokinetic study conducted in Chinese patients (24). There may be other mechanisms affecting imatinib pharmacokinetics. Possibly, the SNPs affect imatinib efficacy might be attributed to affecting the intracellular drug concentrations instead of the plasma concentrations. Also, the sample size of this study is small. Large-scale investigations are needed to clarify the effects of transporter OCTN1, OCTN2, OATP1B3, OATP1A2 and BCRP on imatinib pharmacokinetics.

CONCLUSIONS

This study shows significant relationship between imatinib trough concentrations and CCyR, MMR, CMR among Chinese patients with CML. Furthermore, this study indicates that SLCO1A2 -361G>A polymorphisms significantly affect the CCyR and MMR. These results may be helpful for identifying patients with better clinical response.

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