Introduction

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of the primitive hematopoietic stem cell. It is characterized by the hybrid oncogene BCR-ABL, which codes for the novel BCR-ABL oncoprotein. This oncoprotein has uncontrolled kinase activity that triggers the excessive proliferation and reduced apoptosis of CML cells [1, 2]. Imatinib mesylate (Gleevec, Glivec), a potent and specific inhibitor of the BCR-ABL tyrosine kinase, is now the first-line treatment for CML. Imatinib has significantly improved the prognosis of CML [3]. The International Randomized Study of Interferon and STI571 (IRIS) trial found an estimated cumulative complete cytogenetic response rate (CCyR) and overall survival of 87% and 89%, respectively, among 553 patients who received first-line imatinib therapy for 5 years [4].

Despite the impressive rate of response, some CML patients show primary resistance to imatinib or relapse after an initial response (acquired resistance) [5]. Resistance to imatinib caused by BCR-ABL gene amplification or increased levels of mRNA can be overcome by increasing the imatinib dose [6–8]. More recently, it has been suggested that variations in imatinib trough plasma concentrations (C_{mins}) could affect cytogenetic and molecular responses in CML. Picard et al [9] reported that imatinib C_{mins} were associated with both CCyR and major molecular response (MMR) to standard-dose imatinib (400 mg daily). A subanalysis of the IRIS trial indicated that patients with high imatinib exposure had better rates of CCyR and MMR [10]. Singh et al [11] also reported that the mean C_{mins} of imatinib responders were significantly higher than those of non-responders. However, it was also reported that there was no correlation between mean C_{mins} and CCyR or MMR [12].

The pharmacokinetics of imatinib has been extensively studied in Caucasian CML patients, and very recently Sakai et al [13] found that a lower dose of imatinib could maintain enough imatinib C_{mins} and provided excellent results for the treatment of CML in a Japanese registry. However, few stud-
ies have been reported in a Chinese population. In the present study, we measured steady-state \( C_{\text{min}} \) in CML patients who received imatinib for at least 12 months (400 mg or 600 mg daily) and described the pharmacokinetic features of Chinese CML patients. We assessed how Chinese patients’ characteristics correlated with imatinib \( C_{\text{min}} \), and how imatinib \( C_{\text{min}} \) correlated with complete molecular response (CMR). Finally, a rough comparison between Chinese patients and the patients of the IRIS was performed to gather clues to the optimal initial imatinib dose for Chinese CML patients.

**Materials and methods**

**Patients**

The study was conducted in accordance with the Declaration of Helsinki, and all patients provided written informed consent. Ethics approval was obtained from the Independent Ethics Committee of Union Hospital, Tongji College, Huazhong University of Science and Technology. All CML out-patients who visited the hospital between the 1st and 31st of October 2008 were considered for our study. Inclusion criteria were a) first chronic-phase or accelerated-phase CML treated orally with standard-dose imatinib (400 mg and 600 mg once daily for chronic-phase and accelerated-phase CML, respectively) and b) imatinib treatment duration ≥12 months. In total, 160 CML patients were considered for participation in the study. Exclusion criteria were a) blast crisis before or during imatinib therapy, b) blood collection performed out of the trough concentration time limits, c) poor compliance with treatment, or d) identification of gene mutation(s) in the kinase domain of BCR-ABL.

Of those considered, 114 patients were excluded because of inadequate blood collection performed out of time limits, use of a nonstandard drug dose, recognized poor compliance with therapy (one patient) or progression to blast phase (two patients). Ultimately, 46 patients with CML were included for investigation: 36 and 10 were treated with 400 mg and 600 mg imatinib daily, respectively. All patients were in chronic phase, except two patients treated with 600 mg IM daily in accelerated phase. There were 30 male and 16 female patients. Median age was 38 years (range, 17–79 years). The mean body weight was 61.72±9.67 (SD) kg (median, 60.00 kg; range, 40.0–85.0 kg), and the mean body surface area (BSA) was 1.72±0.14 m² (median, 1.61 m²; range, 1.36-1.97 m²). The median duration of imatinib therapy at the time of \( C_{\text{min}} \) testing was 28.57 months (range, 12–74 months).

**Sample collection and disease response analysis**

Bone marrow was aspirated from the posterior iliac crest of the patients for cytogenetic evaluation. This was performed at diagnosis and every 6 months for the first 2 years, and then yearly thereafter, unless clinical or laboratory features suggested disease progression. CCyR was defined as all 20 bone marrow metaphases analyzed being Ph-.[14] However, because of frequent failure of bone marrow aspiration in CML patients receiving imatinib therapy, collection of bone marrow was severely disrupted. Thus, owing to limited data collection, the correlation between \( C_{\text{min}} \) and achievement of CCyR was not shown and analyzed.

To assess molecular responses, we extracted total RNA from peripheral blood cells and quantified BCR-ABL transcript concentrations using real-time quantitative reverse-transcriptase polymerase chain reaction (RQ-PCR)[15], according to recently proposed recommendations for harmonization of results[16]. CMR was defined as undetectable BCR-ABL transcripts by RQ-PCR. The most recent RQ-PCR results were used to determine molecular response.

**Statistical analysis**

The Student’s t-test or Wilcoxon signed-rank test was used to compare means between the two groups. The chi-square test or Fisher’s exact text was used for comparisons of proportions. Pearson correlation or Spearman’s correlation analysis of \( C_{\text{min}} \) and patients’ characteristics (including age, weight, BSA, time elapsed before imatinib therapy and duration of therapy) was performed in patients treated with 400 mg IM daily.

**Results**

**Imatinib plasma trough concentrations of Chinese CML patients receiving the standard dose**

Thirty-six patients in first chronic phase—23 males and 13 females—were treated with 400 mg imatinib daily. Their mean imatinib \( C_{\text{min}} \) was 1325.61±583.53 ng/mL, with 44% inter-patient variability. For the 23 males, the mean body weight was 64.70±10.81 kg (median, 63.00 kg; range, 40.0–85.0 kg), and the mean body surface area (BSA) was 1.72±0.14 m² (median, 1.70 m²; range, 1.40-1.97 m²). For the 13 females, the mean body weight was 56.39±6.68 kg (median, 59.0 kg; range, 46.0–65.0 kg), and the mean BSA was 1.55±0.11 m² (median, 1.61 m²; range, 1.36-1.68 m²). For all patients, the median age was 38 years (range, 17–79 years), the mean elapsed time before imatinib therapy was 24.75 months (range, 1–84 months), and the median duration of imatinib therapy at the time of \( C_{\text{min}} \) testing was 28.97 months (range, 12–74 months).

Table 1 shows the clinical characteristics of the 36 patients who were given 400 mg IM daily. Only body weight (\( P=0.017 \)) and BSA (\( P=0.001 \)) were significantly higher in males than in females.

The mean \( C_{\text{min}} \) of the 10 patients treated with 600 mg IM daily was 1550.90±462.63 ng/mL, with 30% inter-patient variability.
Correlation of imatinib plasma trough concentrations with patients' characteristics and molecular responses

After Pearson or Spearman’s correlation analysis, we found no significant correlation of imatinib $C_{\text{mins}}$ with age, time elapsed before imatinib therapy and duration of imatinib therapy. However, female patients had significantly higher imatinib $C_{\text{mins}}$ than male patients (1579.69±510.50 ng/mL vs 1182.00±582.97 ng/mL, $P=0.048$). Because of the limited number of patients, the same correlation analysis was not performed in patients treated with 600 mg imatinib daily. No significant differences were found between patients treated with 400 mg ($n=36$) and 600 mg ($n=10$) imatinib daily (1325.61±583.53 ng/mL vs 1550.90±462.63 ng/mL, $P=0.267$).

As shown in Table 2, patients who received imatinib therapy earlier had a significantly higher likelihood of achieving CMR (time elapsed before imatinib therapy: CMR vs no CMR, 20.57±17.21 months vs 39.38±23.11 months, $P=0.016$). Although the female patients have higher imatinib $C_{\text{mins}}$ than the males, they did not have a significantly higher rate of CMR (77% vs 78%, $P=1.000$). There was no statistically significant difference in imatinib $C_{\text{mins}}$ between patients in the CMR group and the no-CMR group (CMR vs no CMR, 1263.39±532.55 ng/mL vs 1543.38±734.11 ng/mL, $P=0.237$). Interestingly, the imatinib $C_{\text{mins}}$ were higher in the no-CMR group, but this result was not statistically significant (Figure 1).

Comparison of imatinib $C_{\text{mins}}$ between Chinese patients and patients in the IRIS study

Patients in the IRIS study were all treated with 400 mg daily. The mean $C_{\text{mins}}$ of male patients, female patients and all patients were 921±531, 1078±515, and 979±530 ng/mL, respectively[10]. As shown in Table 3, the mean imatinib $C_{\text{min}}$ of the

Table 1. Patient clinical parameters according to their molecular response to 400 mg imatinib daily.

| Characteristics                  | All patients | Female patients | Male patients |
|----------------------------------|--------------|-----------------|---------------|
| Number of patients               | 36           | 13 (36)         | 23 (64)       |
| Age (years)                      | 38 (17–79)   | 42 (22–79)      | 36 (17–64)    |
| Body weight (kg)                 | 61.69 (40–85)| 56.39 (46–65)   | 64.70 (40–85) |
| BSA (m²)                         | 1.67 (1.36–1.97) | 1.55 (1.36–1.68) | 1.72 (1.40–1.97) |
| Time elapsed (months)            | 24.75 (1–84) | 22.38 (1–84)    | 26.09 (1–66)  |
| Duration (months)                | 28.97 (12–74)| 33.77 (12–65)   | 22.26 (12–74) |
| Molecular response               |              |                 |               |
| CMR                              | 28/36 (78)   | 10/13 (77)      | 18/23 (78)    |
| No CMR                           | 8/36 (22)    | 3/13 (23)       | 5/23 (22)     |
| Trough imatinib plasma concentration (ng/mL) | 1325.61 (363–2900) | 1579.69 (798–2360) | 1182.00 (363–2900) |

Table 2. Patient clinical parameters according to their molecular response to 400 mg imatinib daily.

| Variable                        | CMR ($n=28$) | No CMR ($n=8$) | $P$ value |
|---------------------------------|--------------|----------------|-----------|
| Imatinib plasma trough concentrations (ng/mL) | 1263.39±532.55 | 1543.38±734.11 | 0.237     |
| Age (years)                     | 38.39±12.35  | 39.38±14.18    | 0.849     |
| Weight (kg)                     | 62.54±9.72   | 58.75±12.17    | 0.365     |
| BSA (m²)                        | 1.67±0.14    | 1.61±0.18      | 0.338     |
| Time elapsed (months)           | 20.57±17.21  | 39.38±23.11    | 0.016     |
| Duration (months)               | 30.14±13.86  | 24.88±20.50    | 0.401     |
patients in the present study seem to be higher than that of the IRIS study (1325.6±583.53 ng/mL vs 979±530 ng/mL), and the patients’ body weight and BSA also seem to be significantly different between the two studies.

**Discussion**

The pharmacokinetics of imatinib has been extensively studied in Caucasian CML patients. However, few studies have been reported on naïve Chinese. Recently, Wang et al. reported the effects of imatinib on the pharmacokinetics of metoprolol, a CYP2D6 substrate, in Chinese patients with CML. Although the authors paid more attention to the pharmacokinetics of metoprolol than imatinib, the study suggested significant differences between Caucasian and naïve Chinese patients treated with 400 mg imatinib daily. It suggested that the plasma $C_{\text{max}}$ and AUC values of imatinib observed in Chinese patients—4245 ng/mL and 39 041 ng·mL$^{-1}$·h$^{-1}$, respectively—were approximately 15% higher than those in Caucasian patients receiving the same dose (800 mg daily) in the phase I study, 3702±1434 ng/mL and 34 200±14 900 ng·mL$^{-1}$·h$^{-1}$, respectively. The estimated effective half-life was approximately 25 h, somewhat longer than the approximately 20 h for Caucasian patients. The clearance in Chinese patients (11.3 L/h) appeared to be in the lower end of the values reported for Caucasian patients, between 10 and 14 L/h. Our data provided the mean imatinib $C_{\text{min}}$ for Chinese CML patients treated with 400 mg or 600 mg imatinib daily. We also found that female CML patients treated with 400 mg imatinib daily had significantly higher $C_{\text{min}}$ than males ($P=0.048$), a disparity that may originate in differences in body weight and BSA, as reported; however, no correlations were found in the other characteristics of the patients with imatinib $C_{\text{min}}$.

In the correlation analysis of disease responses with patients’ characteristics, molecular responses to 400 mg imatinib daily are correlated only with time elapsed before imatinib therapy. It suggests that taking imatinib as soon as possible helps to achieve CMR. Our data agree with the conclusion that imatinib $C_{\text{min}}$ are not correlated with molecular response. An odd result was that the mean imatinib $C_{\text{min}}$ in our patients were a little higher in the no-CMR group than in the CMR group ($P=0.237$). Picard et al. concluded that imatinib plasma trough concentrations were correlated with both cytogenetic and molecular responses to standard-dose imatinib in CML, and the plasma threshold for $C_{\text{min}}$ was set at 1002 ng/mL because it provided the best discrimination potential for achieving MMR. This conclusion was supported by other studies. The inability to find a significant difference between patients in the CMR group and the no-CMR group is probably due to the fact that all of our patients had exceeded the plasma threshold of 1002 ng/mL, and this can in part explain why the patients treated with 600 mg imatinib daily didn’t have significantly higher $C_{\text{min}}$ than patients treated with 400 mg daily ($P=0.267$).

In the rough comparison of imatinib $C_{\text{min}}$ between Chinese patients and IRIS patients, similar results were found in Chinese and Caucasian patients, such as the large interpatient variability in imatinib $C_{\text{min}}$ and higher imatinib $C_{\text{min}}$ in female patients due to lower body weight and BSA. As other reports have explained, the reason for the interpatient variability in imatinib $C_{\text{min}}$ may be the intrinsic variability of the CYP system and drug efflux/influx transporters, such as P-glycoprotein (P-gp or ABCB1), breast cancer resistance protein (BCRP or ABCG2), multidrug resistance protein 1 (MRP1 or ABCC1) and human organic cation transporter-1 (OCT1). The difference in imatinib $C_{\text{min}}$ between Chinese and Caucasians patients was unavoidable. The difference between the results of the present study and IRIS seems to be due to different body weight and BSA. Our findings, which are in agreement with the only finding in Chinese CML patients, suggest that imatinib exposure in Chinese CML patients was higher than in Caucasian patients.

It was reported that dose intensity was critical to optimize response in CML. Based on higher drug exposure in Chinese patients and dose-proportional imatinib exposure, a rational conjecture is that Chinese patients would have a better disease response. We can infer that the patients in our studies had better disease responses, even though CMR was not monitored in the IRIS study, in which BCR-ABL transcripts in the blood samples were measured only at 1 and 4 years in 124 patients who had a CCyR. After 1 year, levels of BCR-ABL transcripts had fallen by at least 3 log in 66 of 124 patients (53%); after 4 years, levels had fallen in 99 of 124 patients (80%). In our study, after a mean follow-up of 28.97 months (range 12–84 months), no BCR-ABL transcripts were detected in 78% of the patients treated with 400 mg imatinib daily regardless of whether they acquired CCyR. However, because of the small number of patients, this conclusion requires further investigation. Another reason that we could not report the exact CMR rate of the patients in our hospital was that some patients with suboptimal response received a dose escalation from 500 mg to 800 mg daily.

Higher drug exposure also leads to more adverse events.

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**Table 3.** Patient clinical parameters according to their molecular response to 400 mg imatinib daily.

|                      | Chinese (n=23) | Male (n=221) | IRIS (n=13) | Female (n=130) |
|----------------------|---------------|--------------|-------------|----------------|
| Mean $C_{\text{max}}$ (ng/mL) | 1182.0±582.97 | 921±531 | 1579.6±510.50 | 1078±515 |
| Body weight (kg)     | 64.7±10.81    | 85.9±16.8 | 56.3±6.68 | 72.4±18.1 |
| BSA ($m^2$)          | 1.72±0.14     | 2.0±0.2   | 1.55±0.11 | 1.8±0.2    |
As we previously reported, in CML patients treated with a standard dose of imatinib, grade 3 leukocytopenia occurred in 16.0% of the patients and grade 3 thrombocytopenia occurred in 18.0% of the patients, respectively.[28] In Japanese studies, grade 3 or 4 neutropenia and/or leukocytopenia occurred in 33.3% of patients, and grade 3 thrombocytopenia occurred in 12.8% of patients.[29] Given Asians’ lower body weight and BSA, both Korean and Japanese doctors doubted whether 400 mg daily of imatinib was an optimal initial dose for Asian patients and proposed a lower dose.[30-34]. We found that the imatinib plasma trough concentration of Chinese patients who received 400 mg imatinib daily was higher than that of Caucasian patients, which provides convincing proof that Asian patients with lower body weight or BSA need a lower dose of imatinib than Caucasian CML patients.

In summary, our work provides a study of the pharmacokinetics of imatinib in Chinese CML and suggests that receiving imatinib treatment as soon as possible is helpful to achieve CMR. Imatinib C_{min} are not correlated with molecular response in Chinese CML patients in chronic phase treated with 400 mg imatinib daily. Chinese CML patients seem to have higher imatinib C_{min} than Caucasian CML patients, which probably results in a better disease response. However, it causes more severe adverse events, and so the optimal initial imatinib dose for Chinese patients requires further investigation.

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Author contribution
Yong YOU, Ping ZOU, and Zhi-chao CHEN designed the research; Qiu-bai LI, Chao CHEN, and Hong-xiang WANG performed the research; Chao CHEN and Yan-lin WU analyzed the data; Qiu-bai LI and Chao CHEN wrote the paper.

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