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Association of Imatinib Plasma Concentration and Single-nucleotide Polymorphisms with Adverse Drug Reactions in Patients with Gastrointestinal Stromal Tumors

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Abstract

Gastrointestinal stromal tumors (GIST) are the most prevalent mesenchymal tumors of the digestive tract. To investigate the association of imatinib mesylate plasma concentration with adverse drug reactions (ADRs) and influences of genetic polymorphisms on ADRs in GIST patients taking imatinib, a cohort of GIST patients consecutively treated with imatinib were included in the observational study. Clinical, pathologic and genotype information was recorded at enrollment and blood samples were collected at time as design. The plasma concentration of the imatinib was detected by LC-MS/MS. A questionnaire was used to evaluate the ADRs at each visit. SNPs in 13 genes were analyzed for a possible association with ADRs. The mean plasma trough concentration of 129 patients taking imatinib was 1.45 ± 0.79 μg/ml, average peak concentration was 2.63 ± 1.07 μg/ml. The imatinib concentration in patients treated with 600 mg/day was significantly higher than other dosage groups ($P < 0.05$). The ADRs were mostly mild. Edema, vomiting, and fatigue were significantly correlated with imatinib concentration ($P < 0.05$). Mutations of *IL13 rs1800925* and *CXCL14 rs7716492* were related with the incidence of leukopenia and rash in our research, separately ($P < 0.05$). We confirmed that with the increase of imatinib concentration, the incidence of edema, vomiting, and fatigue rises as well. Mutations of *IL13 rs1800925* and *CXCL14 rs7716492* may be the promising biomarkers to predict the ADRs of imatinib. The results of the study are of guiding significance for the use of imatinib in patients with GIST. *Mol Cancer Ther; 17(12); 2780–7. ©2018 AACR.*

Introduction

Gastrointestinal stromal tumor (GIST) arising from the interstitial cells of Cajal is the most common sarcoma of the gastrointestinal tract (1–2). According to a domestic research in 2011, the age-standardized GIST incidence rate was 3.6 per 1 million. While the incidence of GIST in Sweden was 14.5 per 1 million, in the United States was 6.8/1 million in 2005 (3–6). The median age of patients with GIST is mostly over 60 years old in Europe, and that in China is around 55 years old (4–6). Because of the presence of *KIT* or *PDGFRA* mutations in the majority of patients with GIST, imatinib mesylate, a selective tyrosine kinase inhibitor (TKI), has been written into consensus at home and abroad as the first-line treatment for patients with GIST (7–9). Consummate pathologic examination and genetic testing can predict the efficacy of imatinib mesylate for patients with GIST, especially with the *KIT* and *PDGFRA* mutations (10–13). The response rate to imatinib in patients with GIST with *KIT* exon 9 mutations is 48%, approximately as half as that of patients with exon 11 mutations (83.5%). In addition, patients with the exon 18 $PDGFRA^{D842V}$ mutation and *KIT-PDGFRA* wild-type GIST are primarily resistant to imatinib (13–16), whereas the percentage of response or stable disease is controversial in different studies. For patients with high-risk GIST, the recurrence-free survival rate was lower with increasing tumor size, small bowel site, *KIT* exon 9 mutation, high mitotic rate, and older age (17). Moreover, adjuvant imatinib in patients with primary GIST who are at high risk of recurrence prolongs overall survival compared with that of historical controls. As for the duration of treatment, illustrated in a randomized clinical trial (SSGXVIII/AIO) was the result that patients with high risk of recurrence administering postoperative imatinib for 36 months have longer relapse-free survival and overall survival time than those administering postoperative imatinib for 12 months (18). On the basis of these evidences mentioned above, latest NCCN guideline for GIST points out that postoperative imatinib

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for at least 36 months should be considered for high-risk patients (8). In the context of long-term postoperative use of imatinib to prevent the recurrence and metastasis of GIST, monitoring imatinib plasma concentrations and adverse drug reactions (ADR) is particularly important.

According to literature reviews and our clinical experience, we found that patients with GIST were generally well-tolerated with imatinib (19). DeMatteo and colleagues conducted a randomized phase III, double-blind, placebo-controlled, multicenter trial about patients with GIST treated with imatinib (20), showing that grade I and II adverse events were common and mostly involved gastrointestinal effects, headache, rash, edema, fatigue, and myalgias/arthralgias. However, the correlation between plasma concentration and adverse events of patients postoperative imatinib administered is rarely reported.

The relationship between SNPs in specific genes and TKI-induced ADRs has been revealed in several studies (21–23). Nielka and colleagues reported that the incidence of leukopenia was increased when the T allele in *FLT3 738T/C* or the G allele in *CYP1A1 2455A/G* were present or CAG in the *NR1I3* haplotype was absent in patients treated with sunitinib (21). For patients with GIST administrated with IM, Liu and colleagues found that subjects of CC in *NR1I2rs3814055* had significantly higher risk of edema (22). On the basis of the researches above, 25 SNPs in 13 candidate genes were determined to analyze a possible association with ADRs in patients with GIST treated with imatinib.

In previous study, our results demonstrated that high concentration of imatinib might lead to leukopenia and hepatic dysfunction (24), which, however, has some limitations because of the small sample size and insufficient evidence. Accordingly, we performed the phase IV prospective observational trial aiming to explore the association of IM plasma concentration with ADRs and influences of genetic polymorphisms on ADRs in patients with GIST taking imatinib.

Materials and Methods

Patient eligibility

Patients aged 18–75 with pathologically confirmed GIST and treated with imatinib were eligible. All patients were generally in good condition with no major organ disease and treated with imatinib for at least 4 weeks. Recurrence risk assessment of them was all intermediate or high risk. Exclusion criteria included noncompliance, active infection, pregnancy, or lactation. Patients involved in other clinical research simultaneously or within 4 weeks before enrollment were also excluded.

The research protocol and ethical application were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Nanjing, China). All patients have signed the informed consent when entering the group. Ethical batch number was 2013-SR-142. The study was conducted following the ethical principles of the Declaration of Helsinki.

Study design

This was a single-center, observational phase IV trial performed between December 2014 and November 2017. A special medical record was set up for each patient enrolled in our study. The clinical information, pathology examination, and genetic detection results were recorded at recruitment. The study was registered at the Chinese Clinical Trial Registry and the registration number was ChiCTR-RNC-14004667.

Study drug administration and risk stratification

Patients were recommended to receive adjuvant IM (Gleevec, Novartis Pharmaceuticals) at a dose of 400 mg/day. The recommended time for imatinib treatment of intermediate-risk and high-risk patients was 1 year and 3 years, respectively. Patients with GIST harboring *KIT* exon 9 mutations were advised to take an initial dose of 600 mg/day. In addition, patients with disease progression or postoperative recurrence were given the recommendation of increasing the original dose to 600 mg/day. Imatinib 800 mg/day or second-line medicine was recommended for patients who had no response to 600 mg/day. If intolerant to imatinib or suffering from serious adverse events, patients were suggested to reduce the dose to 200–300 mg/day, even discontinue the imatinib treatment.

For patients with GIST, the prognosis is commonly stratified according to the NIH consensus classification system based on tumor size and mitotic count (25). However, the NIH stratification does not take the location of GIST and tumor rupture into consideration. In this study, we evaluated the risk of patients according to the Modified NIH criterion (26).

Information and samples collection

At the first month and every 3 months after enrollment, patients were requested to come to our hospital for the imatinib plasma concentration detection. Each time, we collected two heparin anticoagulant tubes of venous blood, each tube containing 6–8 mL venous blood. Blood was drawn before and 3 hours after their administration of imatinib. After the collection, we harvested the upper plasma after centrifuging at 3,000 rpm, 4°C for 10 minutes. All plasma was stored at −80 °C to be tested.

Plasma concentration detection

All samples were detected in the First Affiliated Hospital of Nanjing Medical University (Nanjing, China). The imatinib trough plasma concentration (C_{min}) and peak plasma concentration (C_{max}) were determined using LC-MS/MS, as described previously (21). The lower limit of quantification is 10 ng/mL. At least three independent experiments for each sample were performed.

ADR assessment

According to the NCI adverse event evaluation criteria CTCAE3.0 (27), we made the ADRs evaluation form for patients with GIST. Our doctors recorded and assessed the level of adverse events at each follow-up. If the patients had serious side effects, he/she would be assigned to the specialist clinic for treatment. Besides that, patients with severe ADRs would be regularly followed-up until stable.

DNA extraction and genotyping

Total genomic DNA from whole blood sample was extracted by Commercialized Kits (RelaxGene blood DNA system, Tiangen) according to the manufacturer's instructions. Twenty-five polymorphisms in 13 genes involved in leukopenia, edema, and rash which are the most comment ADRs of imatinib mesylate were selected. Candidate genes and related polymorphisms are listed in Supplementary Table S1. After the DNA extraction, all samples

were sent to Sangon Biotech (Shanghai) Co., Led. for genetic polymorphisms detection.

Statistical analysis

SPSS 20.0 software was used for statistical analysis. Plasma concentration of imatinib was expressed as mean ± SD ($\bar{x}$±s). On the basis of a multicenter research (28), we used the plasma concentration results at 1 month after recruitment to illustrate the correlation between plasma concentration and ADRs. The correlation between the imatinib plasma concentration and side effects was analyzed by Spearman correlation analysis. χ^2 or Fisher exact tests was employed to analyze the statistical differences of imatinib mesylate–induced ADRs and genotypes of each SNP. For $P < 0.05$, the difference was considered statistically significant.

Results

Patients and follow-up

From December 2014 to November 2017, a total of 129 patients with pathologic diagnosis of GIST were enrolled, including 56 males and 73 females, with an average age of 56.98 (range, 29–75 years). The primary sites were stomach (47.29%), small intestine (31.78%), and colorectal (6.98%). Among the 129 patients, 30 patients (23.26%) were at intermediate risk and 99 patients (76.74%) were at high risk. More demographic data and baseline clinical characteristics are summarized in Table 1.

The median follow-up was 21 months, ranging from 6 to 42 months. In our study, the dosage of 27 patients (20.93%) were (20.93%) reduced to 200 or 300 mg/day due to unbearable adverse events. Two patients (1.55%) discontinued for severe leukopenia and interstitial pneumonia, respectively, and the longest discontinuation was 45 days. They continued to take the original dose of imatinib after remission. Of all patients, 3 of them (2.33%) were advised to increase dose to 600 mg/day because of disease progression, 5 patients (3.88%) died during imatinib treatment for 10–23 months. Except for 5 cases of death, no patients were lost to follow-up.

Plasma concentration of imatinib

The mean C_{min} of 129 patients with GIST taking imatinib was 1.45 ± 0.79 μg/mL (range, 0.26–5.13 μg/mL), average C_{max} was 2.63 ± 1.07 μg/mL (range, 0.72–7.63 μg/mL). Figure 1A and B are histograms of imatinib plasma concentration distribution in 129 patients with GIST. The imatinib plasma concentration distribution of patients with different doses is shown in Fig. 2. In terms of C_{min} and C_{max}, there was no significant difference among the 200 mg, 300 mg, and 400 mg dosage group ($P > 0.05$). On the contrary, both C_{min} and C_{max} of 600 mg dosage group were significantly higher than other groups (C_{min}, $P < 0.001$; C_{max}, $P < 0.01$).

As for patients with GIST with distinct *KIT* and *PDGFRA* genotypes, the variations of C_{min} and C_{max} in different groups are shown in Fig. 3. For the reason that the number of patients with wild-type *KIT-PDGFRA*, *KIT* exon 17, and *PDGFRA* exon 12 mutations was small (3, 4, and 2, respectively), no statistical analysis was included. The C_{min} of patients with *KIT* exon 9 mutation was significantly higher than *KIT* exon 11 and wild-type mutations ($P < 0.001$, $P < 0.01$). There is no statistical difference between patients with *PDGFRA* 18 and wild-type *PDGFRA* mutations, both C_{min} and C_{max} ($P > 0.05$).

Table 1. Characteristics of 129 patients with GIST

Variable	Number (%)
Mean age, years (range)	56.98 (29–75)
Gender	
Male	56 (43.41)
Female	73 (56.58)
Localization	
Stomach	61 (47.29)
Small intestine	41 (31.78)
Colorectum	9 (6.98)
Other	18 (13.95)
Risk stratification	
Intermediate risk	30 (23.26)
High risk	99 (76.74)
Mutations	
KIT Exon 11	97 (75.19)
KIT Exon 9	9 (6.98)
KIT Exon 17	4 (3.10)
Wild-type KIT	7 (5.43)
PDGFR Exon 18	6 (4.65)
PDGFR Exon 12	2 (1.55)
Wild-type *PDGFRA*	109 (84.50)
Wild-type *KIT-PDGFRA*	3 (2.33)
Undetected	12 (9.30)
Tumor histology	
Epithelioid	20 (15.50)
Spindle	98 (75.97)
Mixed	11 (8.53)
R0 resection	125 (96.89)
Rupture	3 (2.33)
IHC (positive rate)	
CD117	127 (98.45)
CD34	119 (86.8)
Ki-67	95 (73.64)
SMA	26 (20.16)
S-100	11 (8.53)
Imatinib dose (mg/day)	
200	6 (4.65)
300	21 (16.28)
400	90 (69.77)
600	12 (9.30)

ADRs in patients taking imatinib

By sorting out and analyzing the ADRs evaluation forms of patients with GIST, we found that the majority of ADRs were grade I–II. The incidence of ADRs in 129 patients with GIST taking imatinib is summarized in Table 2. Apart from the adverse events mentioned in Table 2, we found 2 patients (1.55%) with grade III interstitial pneumonia, 6 patients (4.65%) with mild alopecia, 7 patients (5.43%) with neurologic disorder, and 1 patient (0.78%) with grade III anemia. In general, serious ADRs were relatively rare. In our study, 2 patients (1.55%) with hepatic dysfunction, rash and edema, respectively, were evaluated as grade III. Because a small quantity of patients suffered from high-grade adverse events, stratification analysis was no longer performed.

Correlation between imatinib plasma concentration and ADRs

The correlation between imatinib plasma concentration and ADRs is shown in Table 3. Edema, vomiting, and fatigue were all significantly correlated with imatinib plasma concentration ($P < 0.05$), both C_{min} and C_{max}. The Spearman correlation coefficients between above side effects and C_{min} were 0.180, 0.174, and 0.183, and that between adverse events and C_{max} were 0.209, 0.225, and 0.211. Liver dysfunction, leukopenia, rash, and vomiting and plasma concentration were not significantly

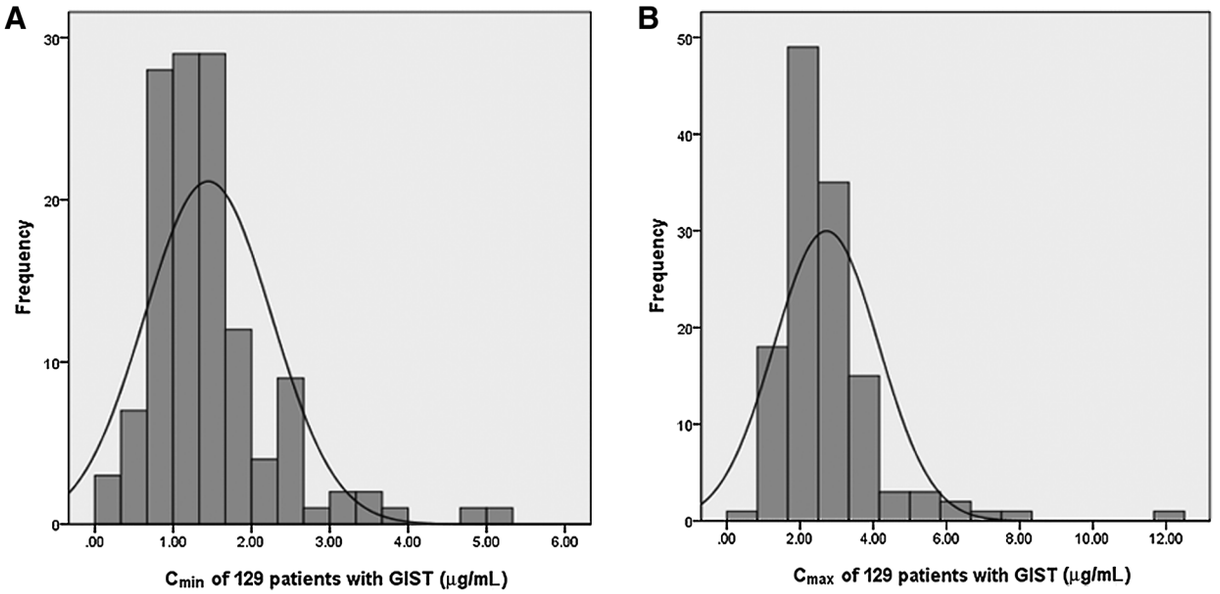

Figure 1.
The distribution of imatinib plasma concentration in 129 patients with GIST histogram was used to describe the plasma concentration of 129 patients. **A,** The C_{min} of 129 patients with GIST. **B,** The C_{max} of 129 patients with GIST.

correlated ($P > 0.05$), both trough and peak concentration. During the follow-up, we found that patients with severe ADRs were gradually relived after reduction or withdrawal.

Effect of genetic polymorphisms on imatinib mesylate–induced ADRs

As shown in Table 1, the top three ADRs were edema, leukopenia, and rash in patients with GIST with imatinib mesylate. We used blood samples from 65 patients with GIST to analyze the association of SNPs with the risk of leukopenia and edema, while only 37 patients with GIST were involved in the analysis of SNPs in rash because of the low incidence. Sixteen SNPs with heterozygous mutations are summarized in Table 4, while other SNPs which were only found in wild-type and homozygous mutation are listed in Supplementary Table S2. For all candidate SNPs, only mutations of *IL13 rs1800925* and *CXCL14 rs7716492* were related with the incidence of leukopenia and rash in our research, separately ($P < 0.05$). The incidence of leukopenia in wild-type

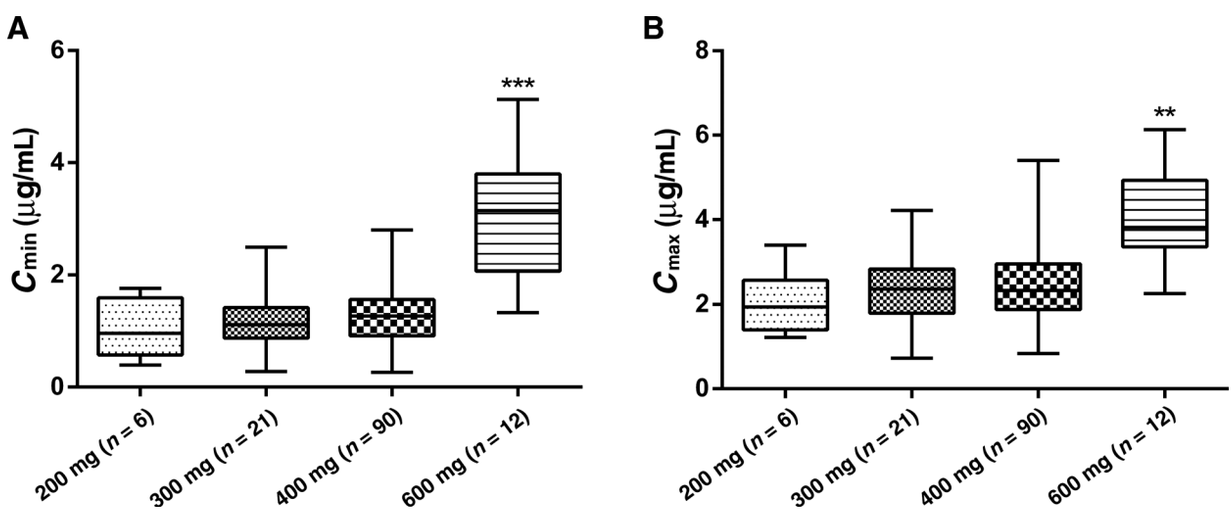

Figure 2.
The distribution of imatinib plasma concentration in different dose groups. **A,** The distribution of imatinib C_{min} in different dose groups. The C_{min} of 600 mg/day group was significantly higher than other groups ($P < 0.001$), no significant difference in the C_{min} of 200, 300, and 400 mg/day groups ($P > 0.05$). **B,** The distribution of imatinib C_{max} in different dose groups. The C_{max} of 600 mg/day group was significantly higher than other groups ($P < 0.01$), no significant difference in the C_{max} of 200, 300, and 400 mg/day groups ($P > 0.05$).

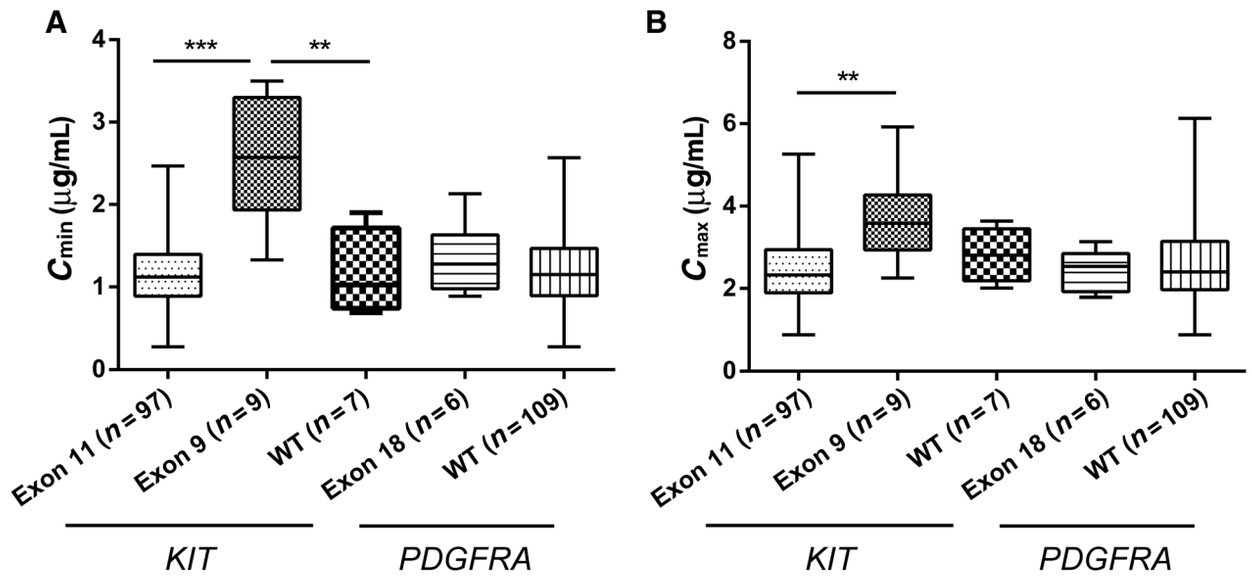

Figure 3.

The distribution of imatinib plasma concentration in different genotype groups. **A,** The distribution of imatinib C_{min} in different genotype groups. The exon 9 mutation group was significantly higher than other groups in patients with *KIT* mutations (exon 11 vs. exon 9, $P < 0.001$; exon 9 vs. wild-type (WT), $P < 0.01$), no significant difference in the patients with *PDGFRA* exon 18 mutations and wild-type *PDGFRA* group ($P > 0.05$). **B,** The distribution of imatinib C_{max} in different genotype groups. The exon 9 mutation group was significantly higher than patients with *KIT* exon 11 mutations ($P < 0.01$), no significant difference in the patients with PDGFRA exon 18 mutations and wild-type PDGFRA group ($P > 0.05$).

(CC; 50%) in *IL13 rs1800925* was significantly higher than in mutate allele T carriers [CT+TT; 19.05%; $P = 0.017$; odds ratio (OR) = 0.235; 95% confidence interval (CI), 0.068–0.812]. With regard to skin rash, we observed an increased risk of rash in carriers of the variant allele of *CXCL14 rs7716492* C>A (17.65% vs. 55.00%, $P = 0.040$; OR, 5.704; 95% CI, 1.239–26.255). For the incidence rate of edema, there is no significant difference in selected SNPs ($P > 0.05$).

Discussion

To date, study of large samples on the correlation between plasma concentration and ADRs in patients with GIST taking imatinib is relatively rare. In this study of 129 patients with GIST in China, we found the most common adverse reaction after imatinib treatment was edema (51.94%), next came leukopenia (40.31%) and rash (24.81%). Compared with the results of a phase III clinical trial (20), the incidence rate of edema has decreased (51.94% vs. 76.9%), while that of leukopenia has increased (40.31% vs. 18.10%). The incidence rate of rash is comparative (24.81% vs. 23.70). Besides, the incidence rates of hepatic dysfunction, vomiting, and fatigue are lower than those in foreign research (20). We speculate that the low incidence of edema and fatigue in patients taking imatinib may be related to their subjective feelings because slight edema and fatigue are often difficult to observe and record. Many rare ADRs were noticed, some of which were never reported previously, such as interstitial pneumonia (1.55%), alopecia (1.55%), and nervous dysfunction [dizziness (1.55%), insomnia (1.55%), and headache (0.78%)]. Although most side effects were mild, we noticed that 4 individuals (3.10%) experienced imatinib withdrawal due to two serious ADRs: a sharp decrease in leukocytes and severe interstitial pneumonia, respectively. The longest withdrawal time was 45 days. Overall, our study also suggests that although most of our patients with GIST are well-tolerated with imatinib mesylate, certain severe ADRs require our attention and even urgent treatment.

Table 2. The incidence of ADRs in 129 patients with GIST

Adverse reaction	Number (%)
Hepatic dysfunction	7 (5.43)
Leukopenia	52 (40.31)
Edema	67 (51.94)
Rash	32 (24.81%)
Vomiting	13 (10.08%)
Diarrhea	11 (8.53%)
Fatigue	4 (3.10%)

It is widely acknowledged that detection of plasma concentration of imatinib mesylate is of substantial guiding significance for medication instructions and dosage adjustment for patients with GIST (23). This study clearly points out that ADRs such as edema, vomiting, and fatigue are significantly associated with plasma concentrations, while the incidences rate of liver dysfunction, leukopenia, and rash show no significant correlation with plasma concentration. Considering the subjectivity of certain ADRs and the limitation of sample size in our study, studies with larger sample and objective evaluation criterion of ADRs are necessarily in need. From this experiment, we propose that patients with GIST with high imatinib plasma concentration have higher risk of edema, vomiting, and fatigue.

Genetic polymorphisms have been always recognized as being either predictive or prognostic biomarkers. The candidate SNPs selected in our study were based on researches related to the toxicity or ADRs in patients treated with TKI. For 25 SNPs, we observed a raised incidence of leukopenia in patients of wild-type

Table 3. The correlation between plasma concentration and ADRs

	C_{min}		C_{max}	
Adverse reaction	**R**	***P***	**R**	***P***
Hepatic dysfunction	0.061	0.495	0.043	0.627
Leukopenia	−0.129	0.145	0.006	0.951
Edema	0.180	0.042[a]	0.209	0.017[a]
Rash	0.010	0.914	0.029	0.745
Vomiting	0.174	0.049[a]	0.225	0.010[a]
Diarrhea	0.075	0.396	0.024	0.785
Fatigue	0.179	0.024[a]	0.211	0.016[a]

[a]$P < 0.05$; the adverse reaction is significantly related to the plasma concentration.

of *IL13 rs1800925* ($P < 0.05$), which was opposite to the result from the research on sunitinib-induced leukopenia (23). Moreover, the T allele of *IL13 rs1800925* has been discovered to be related to increased IL13 protein function in the development of allergic asthma (29). To our knowledge, we report for the first time that SNP in IL13 is related to the risk of leukopenia in patients treated with imatinib mesylate. Consistent with the results of Zhuang and colleagues' study on imatinib mesylate (30), this study also shown that the incidence of skin rash in mutate allele A carriers in *CXCL14 rs7716492* was significantly higher than that in wild-type (CC). These biomarkers might be able to predict the risk of a certain ADR in patients taking imatinib mesylate. However, we observed no SNP is related to the incidence of edema in our study. Still, further studies that relate gene polymorphisms to ADRs are needed to confirm our findings and discovery more promising candidate SNPs.

Considering the plasma concentration in patients treated with different doses, the study shows C_{min} and C_{max} of patients with 600 mg/day are highest among all groups of different doses, which is consistent with Yoo and colleagues' study (31). We presume that the saturation effect of liver enzyme metabolism leads to a significant increase in the plasma concentration of imatinib in patients with 600 mg/day. Interestingly, we also find C_{min} and C_{max} of patients with *KIT* exon 9 mutation are significantly higher than other mutations, seemingly indicating that distinct mutations may contribute to the difference in plasma concentration. However, it is also noticed that the dosage of patients with *KIT* exon 9 mutation is 600 mg/day, which means, the cause of the difference is probably the different dosage rather than the genotypes, and there is no obvious correlation with the type of mutations.

Demetri and colleagues reported that when the imatinib plasma trough concentration of patients with advanced GIST below 1,100 ng/mL, the progression-free survival (PFS) would show a significant decline (32). In our study, the plasma trough concentration in 62.02% of patients with GIST was more than 1,100 ng/mL. The result has an advantage over a research of 180 patients

Table 4. Comparison of the incidences of ADRs related to candidate SNPs in 129 Chinese patients with GIST

SNP_ID	Gene	Genotype	*N*	Yes (%)	No (%)	*P*	OR	95% CI
				Edema (*n* = 65)				
rs3814055	*NR1I2*	*CC*	42	21(50.00)	21(50.00)	0.238	0.533	0.187–1.524
		CT+TT	23	8(34.78)	15(65.22)			
				Leukopenia (*n* = 65)				
rs1800925	*IL13*	*CC*	44	22(50.00)	22(50.00)	0.017[a]	0.235	0.068–0.812
		CT+TT	21	4(19.05)	17(80.95)			
rs4073054	*NR1I3*	*CC*	42	17(40.48)	25(59.52)	0.916	0.945	0.334–2.674
		CT+TT	23	9(39.13)	14(60.87)			
rs2307418	*NR1I3*	*AA*	61	25(40.98)	36(59.02)	0.916	0.48	0.470–4.884
		CC	4	1(25.00)	3(75.00)			
rs2307424	*NR1I3*	*CC*	18	7(*38.89*)	11(61.11)	0.910	1.066	0.351–3.243
		CT+TT	47	19(40.43)	28(59.57)			
rs1933437	*FLT3*	*CC*	5	2(40.00)	3(60.00)	1.000	1.000	0.155–6.438
		CT+TT	60	24(40.00)	36(60.00)			
				Rash (*n* = 37)				
rs17885098	*CYP2C19*	*CT*	5	1(20.00)	4(80.00)	0.630	2.737	0.274–27.354
		TT	32	13(40.63)	19(59.38)			
rs884225	*EGFR*	*AA*	4	1(25.00)	3(75.00)	1.000	1.950	0.183–20.827
		AG+GG	33	13(*39.39*)	20(*60.61*)			
rs28557040	*EGFR*	*AA*	31	13(41.94)	18(58.06)	0.376	0.277	0.029–2.660
		AG	6	1(16.67)	5(83.33)			
rs11543848	*EGFR*	*GG*	12	2(16.67)	10(83.33)	0.084	4.615	0.836–25.491
		AG+AA	25	12(48.00)	13(52.00)			
rs712829	*EGFR*	*GG*	30	12(40.00)	18(60.00)	0.687	0.600	0.100–3.612
		TT	7	2(28.57)	5(71.43)			
rs10228436	*EGFR*	*GG*	11	4(36.36)	7(63.64)	0.723	1.500	0.352–6.397
		AG+AA	26	10(38.46)	16(61.54)			
rs2459693	*PIK3CA*	*CC*	4	3(75.00)	1(25.00)	0.142	0.167	0.015–1.794
		CT+TT	33	11(33.33)	22(66.67)			
rs12668095		*GG*	30	12(40.00)	18(60.00)	0.687	0.600	0.100–3.612
		GC+CC	7	2(28.57)	5(71.43)			
rs7716492	*CXCL14*	*CC*	17	3(17.65)	14(82.35)	0.040[a]	5.704	1.239–26.255
		CA+AA	20	11(55.00)	9(45.00)			
rs4796120	*CCL5*	*AA*	18	8(44.44)	10(55.56)	0.508	0.577	0.151–2.207
		AG+GG	19	6(31.58)	13(68.42)			

[a]$P < 0.05$; the differences of the incidence of ADRs between wild-type and mutate allele carriers are significantly.

in Holland (33), where only 33.3% of patients had plasma trough concentration values 1,000 μg/L in all measured sample. Bouchet and colleagues tried to specify a C_{min} threshold value associated with a longer PFS in patients with advanced GIST (28). They finally found out that a C_{min} threshold of 760 ng/mL defined by log-rank test was associated with longer PFS for patients with advanced GIST. There are still some limitations in the study, for example, all patients are classified as advanced GISTs and come from the West. In this study, the distribution of imatinib plasma concentration in Chinese patients with GIST is different from the Western patients. In this regard, the C_{min} threshold value associated with a longer PFS in Chinese patients with GIST is awaiting further exploration.

The observational study still had some shortcomings. On one hand, the mutation information of our patients was limited by their wills and economic status. On the other hand, the sample of our study was small and large sample, multi-center research is needed. Moreover, as to the association of *IL13* and *CXC14* SNPs with leukopenia and skin rash, respectively, an independent cohort is required to confirm. Taken together, this study depicts the distribution of imatinib plasma concentration in patients with GIST, certifies SNPs that related to the incidence of main ADRs of imatinib mesylate, and reveals the ADRs associated with the plasma concentration, such as edema, vomiting, and fatigue. Moreover, we point out the urgency of specifying the effective C_{min} threshold value of imatinib in Chinese patients with GIST.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Q. Zhang, H. Xu, Z. Xu
Development of methodology: Q. Zhang, J. Xu, L. Chen, Y. Wang, H. Xu, Z. Xu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Q. Zhang, J. Xu, Y. Qian, K. Xu, M. Chen, Z. He, L. Yang, D. Zhang, L. Wang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Q. Zhang, J. Xu, Y. Qian, L. Chen, Q. Li, K. Xu, L. Yang, D. Zhang, L. Wang, X. Sun, Y. Wang
Writing, review, and/or revision of the manuscript: Q. Zhang, J. Xu, Z. He, H. Xu, Z. Xu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Q. Zhang, J. Xu, L. Chen, Q. Li, L. Sun, X. Sun, Y. Wang, H. Xu, Z. Xu
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