The Application of Therapeutic Drug Monitoring of Imatinib in the Patients with Gastrointestinal Stromal Tumors (GISTs): A Retrospective Cross-Sectional Study

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Abstract

Aims: The optimal dose of imatinib on survival in the adjuvant treatment of patients with resected GISTs remains unsettled. Therefore, this study aimed to assess the impact of the adjustment of dose based on imatinib plasma trough concentrations (Cmin) on the prognosis of GIST based in the adjuvant setting. Methods: We conducted a retrospective cross-sectional study of GIST patients treated with imatinib. Simultaneously, the blood samples at steady-state of the aforementioned patients were obtained for the determination of imatinib Cmin. Inverse probability of treatment weighting (IPTW) was used for reducing selection bias in baseline characteristics. Kaplan–Meier analyses and multivariate Cox proportional hazards were used to evaluate the association of the different dosages of imatinib with recurrence-free survival (RFS). Results: A total of 79 patients were identified in this study. Of these patients treated with imatinib 200 mg/d (n=8), 300 mg/d (n=33), 400 mg/d (n=37), and 600 mg/d (n=1)the mean±standard deviation (SD) imatinib Cmin was 704±299ng/mL, 1153±473.3ng/mL, and 1246±491.3ng/mL, respectively. Additionally, imatinib Cmin of 200-mg/day group was significantly lower than groups of 300- (P=0.036) and 400-mg/day (P=0.016), no significant difference in the Cmin of 300- and 400 -mg/day group (P=0.427) (Fig 3). Before and after adjustment by propensity score-based IPTW, no significant difference in recurrence-free survival between the Conclusions: Our findings provide a new insight that imatinib Cmin may be used as a potential biomarker, to assist in the evaluation of the safety, and efficacy of individualized dosage adjustments in the adjuvant setting.

1 INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common type of sarcoma derived from the digestive tract and are characterized by the common presence of oncogenic mutations in genes encoding the KIT or PDGFRA receptor tyrosine kinases.1 The advent of imatinib, a tyrosine kinase inhibitor (TKI), has greatly improved the oncological outcomes of GISTs. [1,2] It has been widely validated that the patients with resected GIST at intermediate-, high-risk could benefit from the imatinib adjuvant setting, especially recurrence-free survival (RFS).[3-13] A randomized clinical trial (SSG XVIII/AIO) reported that RFS was significantly better in 3 years of imatinib when compared with 1-year arm, indicating that prolonged the duration of imatinib adjuvant therapy leading to improving the prognosis of these patients.[10] Furthermore, it has been reported that about 50% of deaths may be avoided during the first 10 years of follow-up following surgical resection with longer adjuvant imatinib treatment.[13]

However, it is noted that approximately 50% of the patients discontinued imatinib treatment early. Of these, quite a proportion of patients are intolerant to imatinib-related adverse reactions.[10] In real clinical practice, physician usually consider dose reduction for the above patients with GISTs to alleviate drug toxic effects and the maintenance of imatinib treatment.[14-18]So far, the feasibility of low-dose imatinib adjuvant therapy

remains unknown. Generally, imatinib is initiated at a fixed dose of 400mg/d in the patients regardless of body, which is thought to be a potential contributor to variability in imatinib systemic exposure.

On the other hand, numerous studies have shown that imatinib plasma trough concentration (C_{min}) is significantly associated with the prognosis of GISTs and chronic myelogenous leukemia (CML).[19-21]Furthermore, the patients with a threshold of C_{min} [?] 1100ng/mL have a favorable prognosis when compared to those with C_{min} less than 1100ng/mL.[19] Another real-world study demonstrated that the correlation of threshold of C_{min} 760 ng/mL in patients with prolonged progression-free survival (PFS).[20] Thus, it is necessary to underscore the significance of close clinical monitoring to continue imatinib treatment for patients at intermediate and high risk.

In this case, we conducted a retrospectively cross-sectional study, and collected and analyzed data on patients with resected GIST treated in our institute with imatinib at either 200 mg daily, 300 mg daily, 400 mg daily, or 600 mg daily, to elucidate the impact of different dosages of imatinib on these patients. In addition, the distribution of the imatinib C_{min} at different levels of doses in patients was evaluated in this study. Collectively, the main objective of this study was to explore that imatinib C_{min}, as a biomarker, is used to evaluate the feasibility, safety, and efficacy of the different levels of imatinib doses in the adjuvant treatment setting.

2 MATERIALS

From 2019 to 2020, the patients with histologically confirmed GIST in Sichuan University Gastrointestinal Surgery Center in Chengdu, China, actively participated in this study. Inclusion criteria are as follows: (1) [?]18year-olds with hepatic and renal functions, adequate hematological, histologically proven GIST; (2) Eastern Cooperative Oncology Group performance status (ECOG PS) [?]2; (3) The duration of imatinib adjuvant therapy at least 29days. The study protocol was approved by the medical ethics review boards and performed following the Declaration of Helsinki. All patients provided written informed consent before registration. This trial was registered with the Chinese Clinical Trial Registry and the registration number was ChiCTR1900020854 (*http://www.chictr.org.cn.*). Patients underwent follow-up with enhanced computed tomography or magnetic resonance imaging scans every 6 months for the first 2 years, every 1 year for the next 5 years in the process of imatinib adjuvant therapy. Hematological and non-hematological adverse events were documented and graded in light of CTCAE (Common Terminology Criteria for Adverse Events Version 5.0) v5.0. Moreover, patient medical records were reviewed retrospectively.[22]

Clinical data of patients with GIST, who had been treated with various doses of imatinib (200–600 mg/day) for at least 29 days were collected between December 2019 and November 2020. Within 24±2 h after the last dosage of imatinib, blood samples (at least 3 mL) were collected into heparinized tubes, centrifuged at 3,000 rpm for 10 min at room temperature, and stored at -80degC until analysis. $C_{min}$was measured by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, specific methods have been previously reported.[23] All samples were detected in the Laboratory of Clinical Pharmacology, West China Hospital of Sichuan University (Chengdu, China). In addition, to evaluate the correlations between imatinib C_{min} and different dosages, the patients were divided into four groups according to the imatinib C_{min} quartiles. The lower quartile (Q1) included the 25% of patients with the lowest imatinib C_{min}; Q2 and Q3 indicated the 25 % below and above the median concentration, respectively; Q4 included the 25% of patients with the highest imatinib C_{min}.

Statistical analysis

Pearson χ^2 or Fisher's exact test was used for the comparison of categorical variables, while the Wilcoxon rank-sum test was used for ordinal and continuous variables. Recurrence-free survival (RFS) was the primary endpoint of this study, which was defined as the time from the date of the first dose of imatinib to the date of the first documented tumor recurrence assessed by radiographic imaging or mortality resulting from any cause. Patients who were alive and without the disease-specific recurrence were censored at the last follow-up.

We calculated the inverse probability of treatment weighting (IPTW) method using the propensity scores

for eliminating the effects of confounding and selection bias by creating a pseudo-sample with the method as reported previously. [24,25] To estimate the IP weights, we calculated each patient's probability of imatinib dosage adjustment via application of multivariate logistic regression model, with dosage adjustment of imatinib as the outcome and BSA, age, gender, risk stratification, mutation status, primary tumor site, and imatinib trough concentration (C_{min}) as covariates. The IP weights were then calculated based on each patient's estimated probability of whether dose reduction of imatinib, given their actual regimen of imatinib therapy.

To study the effect of dosage of imatinib adjustment on RFS of resected GISTs, weighted Cox proportional hazard regression models were estimated. Hazard ratios (HRs) along with their 95% confidence intervals (CI) were reported. RFS was calculated by the Kaplan–Meier method and compared by log-rank test. Cox proportional hazard model was used to assess the prognostic factors for the IPTW-matched patients. All statistical analyses were performed by using RStudio (*https://www.rstudio.com/*) in the text of R, version 4.1.2 (R Core Team 2021, Vienna, Austria) (*https://www.r-project.org/*). All tests were two-sided, P-values less than .05 were considered statistically significant.

3 RESULTS

To determine the therapeutic outcomes and safety of adjuvant therapy in the setting, and eventually, a total of 79 GIST patients fulfilling the inclusion criteria were included in this study (Figure 1). As shown in Figure 2, distribution of steady-state imatinib C_{min} of postoperative patients with following imatinib adjuvant therapy at least day 29. Of these patients treated with imatinib 200 mg/d (n=8), 300 mg/d (n=33), 400 mg/d (n=37) and 600 mg/d (n=1), the mean±standard deviation (SD) imatinib C_{min} was 704±299ng/mL, 1153±473.3ng/mL, 1246±491.3ng/mL, and 1621ng/mL, respectively. Furthermore, these patients were divided into four groups four groups based on the levels of imatinib C_{min}. The Q1 (335 to 807 ng/mL; n=20), Q2-Q3 (807 to 1347 ng/mL; n=40), and Q4 (1347 to 2919 ng/mL; n =20). The 8 patients in the 200-mg dose group, five were in Q1, three were in Q2-Q3; for the 33 patients in the 300-mg dose group, 12 patients were in quartile 1 (Q1), 17 were in Q2-Q3, and seven were in Q4; for the 37 patients in the 400-mg dose group, six were in Q1, 19 were in Q2-Q3, and 12 were in Q4. It is noteworthy that the proportion of patients reaching the predefined target C_{min} (1100ng/mL) was comparable between both different dose groups, with 54.1% (20/37) of 400-mg dose group and 48.5% (16/33) of 300-mg dose group reaching the target (P = 0.82). Furthermore, when the predefined target imatinib C_{min} was defined as 760ng/mL, no significant difference was observed between the above-mentioned two groups (55.9% (33/37) vs. 44.7% (26/33), P=0.33). In addition, the steady-state imatinib C_{min} of 200-mg/day group was significantly lower than groups of 300- (P=0.036) and 400-mg/day (P=0.013), no significant difference in the C_{min} of 300- and 400 -mg/day group (P=0.427) (Fig 3A). Additionally, the higher imatinib C_{min} levels in women were observed in the 300 and 400-mg daily groups when compared with males (Fig 3B). On the other hand, we excluded the patients with 200mg/d and 600mg/d because of the limited patients in this study, and eventually, 79 patients were identified for further analysis. The baseline clinical characteristics of the aforementioned patients were shown in Table 1. With regard to the adverse drug reactions (ADRs), as shown in Table 2, the most common mild adverse reactions were periorbital edema (71.4%), followed by muscle cramps (59.5%), nausea and vomiting diarrhea (53.2%), fatigue (35.4%), and et al. Generally, imatinib was well tolerated, while mild-to-moderate ADRs (grade 1 and 2) were found in these patients. The median follow-up for the entire cohort was 51.1 months (interquartile range (IQR), 33.4 to 65.0 months). A comparison of prognostic outcomes in the PTW-adjusted cohort showed no significant difference in RFS between the 300-mg and 400-mg daily groups (Figure4). The median RFS in the 400-mg daily group was 130 months (95% CI 130–not reached) versus not reached for those in the 300-mg daily group (p = 0.47). Additionally, the result of multivariate Cox proportional hazards regression analysis showed that a dose of 300-mg daily has no significant impact on RFS (hazard ratio [HR] 3.5; 95% confidence interval [CI] 0.3-44.1). This is consistent with the result (HR 2.3; 95% CI, 0.2-30.4) after the IPTW-adjusted.

4 DISCUSSION

It is widely acknowledged that measuring the steady-state imatinib C_{min} level of imatinib is of important

guiding significance for medication instructions and dosage individualization for GIST patients.[14-17,19,20] The study conducted by Demetri and colleagues found out that patients with advanced GIST with the threshold of imatinib C_{min} more than 1100 ng/mL have a favorable progression-free survival (PFS) compared to these less than 1100 ng/mL.[19] In this study, the imatinib C_{min} in 51.4 % of patients with GIST was more than 1,100 ng/mL. This outcome is superior to a study in Holland, where only 33.3% of patients had imatinib C_{min} values of 1,000 mg/L in all samples of 180 patients.[26]Additionally, Bouchet et al found a significant correlation between the imatinib C_{min} threshold of 760 ng/mL and longer PFS for patients with advanced GIST.[20]An increasing number of studies have demonstrated that imatinib increases the RFS of GIST patients, while retaining patients on therapy following a radical resection remains challenging because of discontinuation of imatinib therapy occurring in a percentage of patients owing to drug-related adverse events (AEs).[10,16] In addition, the study conducted by Chandrajit P and colleagues reported that women were prone to discontinuation of fixed-dose imatinib of 400mg/d, and had higher imatinib C_{min} levels compared with men, indicating that lower doses could be considered. [9]Although the C_{min} level of imatinib is associated with the prognosis of GIST, it is still undefined that whether individualized dosage adjustments based on the C_{min} level would provide clinical benefits to GIST patients, such as improving the long-term prognosis and reducing imatinib-related toxicity. Additionally, the findings of our study show patients in low-dose arms usually are characterized by elderly female predominance and lower BSA. This is consistent with the research conducted by Yuichi et al.[17] Moreover, no significant differences in RFS and C_{min} levels of 300- and 400-mg daily groups were observed in our study, suggesting that it may be feasible to apply individualized dosage adjustments based on the imatinib C_{min} level. On the other hand, numerous studies have been shown that higher imatinib C_{min} levels are associated with imatinib-related toxicity.[14,16,18] But pharmacokinetic data were too limited to draw any significant correlation of C_{min} with drug toxicity in this study. It is noteworthy that the Chinese and Japanese populations were prone to experience imatinib treatment-related serious adverse events compared with that in the population of European ancestry when with standard dose of imatinib is 400 mg once daily.[17,26,27]

There are still several shortcomings in this study, the mutation information of patients was limited because of economic status and their wills. Therefore, we cannot further investigate the impact of tumor mutational status on long-term oncological outcomes of resected GIST patients with imatinib adjuvant therapy. However, a multi-institutional European retrospective study conducted by Bruno et al found that a daily dose of 800 mg versus 400mg for GIST patients with harboring exon 9 kit mutations did not demonstrate better outcomes in terms of survival results in the post-operative setting, in agreement with the result of a study conducted by Almudena and colleagues.[12] In addition, the result of the ACOSOG Z9001 trial shows that tumor genotype seems did not have a significant impact on the RFS of resected patients at high risk.[5] Besides, the sample of our study was small, and large sample, prospective multicenter research is warranted. Furthermore, it is mandatory to establish the effective threshold of imatinib C_{min} of the Chinese population of GIST patients.

5 CONCLUSIONS

In conclusion, considering the limitations of the retrospective analysis and the small size of the sample, an additional effort should be supported on an international basis to clarify the role of adjuvant therapy in this setting. Even though our study is limited by the selection bias and small size of the sample, we believe that our results should be considered when adjusting the regimen of imatinib for patients who are intolerant to standard-dose imatinib therapy in the absence of a randomized clinical trial.

Figure1. The flow diagram of research cohort inclusion and exclusion.

Figure2. The distribution of C_{min} in different dose groups. The horizontal line represents C_{min} =1100 ng/mL, and the two vertical lines represent 25% and 75% percentiles (1,100 and 2,040 ng/mL), respectively.

Figure3. Association of different doses of imatinib and imatinib plasm trough concentration (C_{min})(A). The group of 600-mg/d was only one patient and thus was excluded. Correlations between imatinib C_{min} and gender in 300-, and 400-mg/d groups(B).

Figure4. Recurrence-free survival in the unmatched (A), and the inverse probability of treatment weight-

adjusted analysis (B) in groups of patients with different doses.

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CONTRIBUTORS

B.Z. and Y.Y. designed the study. J.X. performed the imatinib quantification in plasma. T.W. and J.W. performed the pharmacokinetic and statistical analysis, interpreted the data, and wrote the manuscript. W.W. and J.X. critically reviewed the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests

DATA AVAILABILITY STATEMENT

Research data are not shared.

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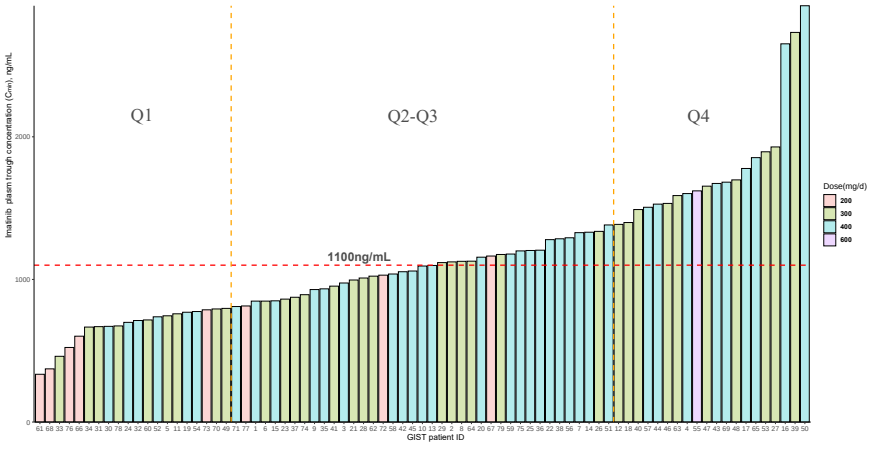

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