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ORIGINAL RESEARCH

Dasatinib Dose Optimization Based on Therapeutic Drug Monitoring in Patients with Chronic-Phase Chronic Myeloid Leukemia

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Background: Although a dosage decrease regimen for chronic phase chronic myeloid leukemia (CML-CP) has been suggested, there is a marked lack of guidance on individualizing medication dosages for patients.

Methods: Our aim was to explore the application of therapeutic drug monitoring (TDM) as a strategy for optimizing dasatinib dosage in patients with CML-CP.

Results: It was observed that patients administered a dosage of 100 mg exhibited significantly higher concentrations than those given 50 mg, with no marked difference in concentration between branded and generic drugs. Further analysis unveiled a robust correlation between peak concentration (C_{max}) and clinical response (major molecular response (MMR): 103.8 ± 54.0 ng/mL versus 48.6 ± 13.9 ng/mL, $P < 0.001$; deep molecular response (DMR): 112.7 ± 57.6 ng/mL versus 66.2 ± 36.1 ng/mL, $P = 0.001$). Patients with a C_{max} >51.85ng/mL were more likely to achieve MMR, while those with a C_{max} surpassing 112.5 ng/mL had a higher probability of attaining DMR. We successfully implemented dasatinib dose reduction based on concentrations without loss of DMR in 22 patients undergoing first-line therapy. Moreover, trough concentrations (C_{min}) >2.48 ng/mL were closely associated with the onset of pleural effusion. Older patients demonstrated higher C_{min} and C_{max}, irrespective of whether they were on a 50 mg or 100 mg dosage regimen.

Conclusion: TDM-based dose optimization could lead to beneficial clinical outcomes for patients with CML-CP. Furthermore, in terms of blood drug concentration, our findings supply additional evidence supporting the first-line treatment regimen of 50 mg daily.

Keywords: chronic myeloid leukemia, dasatinib, dose optimization, therapeutic drug monitoring, clinical response

Introduction

The introduction of tyrosine kinase inhibitors (TKIs), notably imatinib, has revolutionized the treatment of chronic myeloid leukemia (CML).[1] This innovation has extended the life expectancy of CML patients to approximate that of the general population. Dasatinib, an orally administered second-generation TKI, is particularly effective in treating Philadelphia chromosome-positive (Ph^+) CML patients who exhibit resistance or intolerance to previous therapies, including imatinib.[2,3] Dasatinib is associated with unique adverse events (AEs) such as pulmonary hypertension and pleural effusion (PE).[4,5] These side effects significantly impair the patient's quality of life and may even prove fatal. Consequently, there is a growing movement among CML patients towards seeking dose optimization and personalized treatment plans.

Dasatinib is typically initiated at a fixed dose of 100 mg daily for the treatment of patients with chronic phase (CP) CML. Research has revealed a correlation between exposure to dasatinib and response.[6] Nevertheless, pharmacokinetic (PK) exposure to dasatinib varies greatly among patients. Consequently, some patients may encounter therapeutically relevant toxicity due to high exposure, while others may suffer suboptimal efficacy due to low exposure.[7,8] Furthermore, East Asian patients with lower body weights have experienced higher incidences of AEs when given the standard 100 mg

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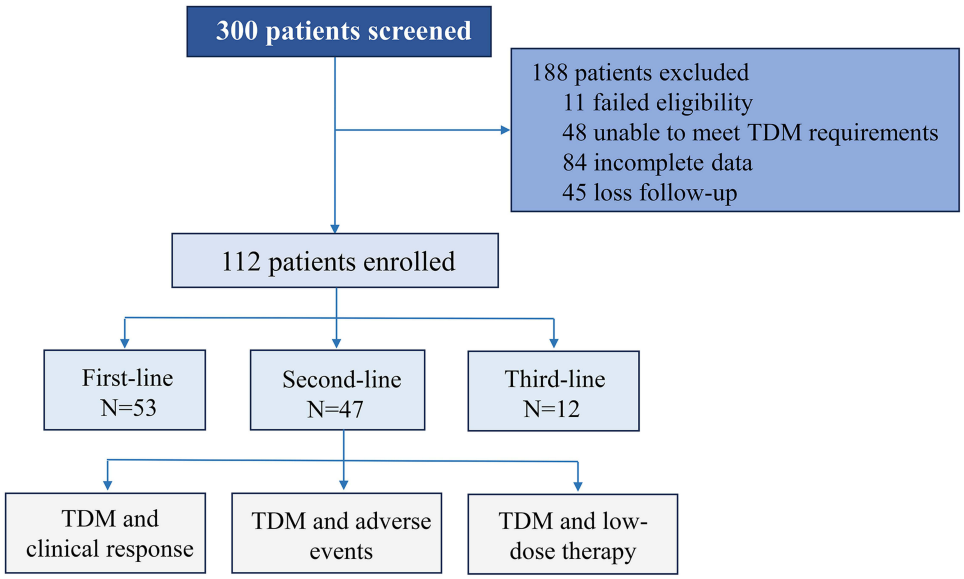
Graphical Abstract



dose of dasatinib.[9] Therefore, it is imperative to determine an appropriate initial dosage of dasatinib based on patient characteristics to address these disparities. Recent studies suggest low-dose dasatinib therapy as an effective and safe regimen for newly diagnosed CML-CP patients.[10,11] Moreover, dose reduction has emerged as a goal for ongoing treatment in certain CML patients who have achieved optimal responses.[12] This strategy can not only decrease AEs but also alleviate the financial strain on patients. However, we currently lack clear indicators to guide low-dose therapy for maximum benefit. Despite the proven efficacy of dasatinib, concerns persist regarding its use.

Therapeutic drug monitoring (TDM) is progressively becoming a practical tool for achieving personalized medicine in patients receiving targeted drugs.[13] As an effective auxiliary strategy, TDM could potentially provide solutions to the current treatment conundrum posed by dasatinib. However, there is yet to be a consensus on the use of TDM in dasatinib therapy, including routine implementation, monitoring indicators, target ranges, and feasibility. In this study, we aim to evaluate the correlation between dasatinib concentration and both clinical response and AEs. Furthermore, we seek to determine the target ranges for clinical responses and PE in an effort to provide additional references for dasatinib dose optimization guided by TDM.

Materials and Methods

Patient Selection

We enrolled patients with CML undergoing dasatinib treatment at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology between January 2018 and December 2021. Eligibility criteria included patients with CML-CP, dasatinib therapy, age above 18 years, and demonstrable compliance (evidenced by timely and accurate daily intake of dasatinib, coupled with regular attendance at follow-up appointments). Patients transitioning to dasatinib within one month of initiating first-line treatment with a TKI were still considered to be receiving first-line treatment. Exclusion criteria included diagnosis at accelerated (in the latest WHO5 classification, accelerated phase CML was removed) or blastic phase, poor compliance, concurrent use of drugs that could affect dasatinib concentration, or incomplete data. The study received approval from the Institutional Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) ([2021] 0784) and was conducted in accordance with the Declaration of Helsinki. Patient demographic profiles, underlying diseases, medication, laboratory findings, AEs, and other clinical information were obtained during regular follow-ups at an outpatient clinic.

Drug Administration

In first-line dasatinib therapy, clinicians typically present clinically appropriate therapeutic options through shared decision-making with patients, who may select to initiate dasatinib at conventional standard dosing. When selecting dasatinib for patients with significant comorbidities or elderly populations, clinicians often recommend initiating at a reduced dose of 50 mg daily, aligning with consensus guidelines such as recommendations for toxicity mitigation. During subsequent-line treatment, the use of dasatinib is often determined by clinicians based on rigorous assessment of the patient's prior treatment history, disease progression patterns, financial circumstances and pharmacodynamic profiling. All patients in the study were administered dasatinib, applied either as frontline therapy or as later lines of treatment. The drug was given orally once daily at a set time, with dosages of either 50 mg or 100 mg. Dose reduction strategies were employed to alleviate AEs, lessen financial strain on patients exhibiting optimal response, or to prepare for therapy discontinuation for patients with sustained optimal response.

Therapeutic Drug Monitoring

Dasatinib displays a distinct pharmacokinetic profile, reaching peak blood concentration (C_{max}) within 2–4 hours post-intake, followed by a rapid decline leading to a residual concentration (trough concentration, C_{min}) at 24 hours.[14] Pharmacological studies have suggested that PE is driven by the C_{min}, while C_{max} is strongly associated with clinical response.[15] After 7–10 days of continuous administration, blood samples were taken half an hour before medication (to measure C_{min}) and two hours post-medication (to measure C_{max}). Patients subjected to dose reductions contributed two concentration datasets (prior and post-adjustment) provided that blood sampling complied with predefined time criteria. A total of 66 and 62 valid dasatinib concentration measurements were obtained for dasatinib at the 50 mg and 100 mg daily, respectively. These samples were centrifuged at 10625 ×g for 10 minutes, after which the plasma was frozen at −80°C. Dasatinib plasma concentrations were determined using high-performance liquid chromatography-tandem mass spectrometry.[16]

Response Assessment

CML-CP was characterized by the presence of fewer than 10% blasts in the peripheral blood or bone marrow, and the absence of extramedullary involvement. The clinical response of patients to treatment was monitored through both cytogenetic and molecular tests, which were used to measure BCR::ABL1 mRNA levels on the international scale (IS). The optimal, warning and treatment failure were evaluated on the basis of 2020 ELN guideline.[17] A complete cytogenetic response (CCyR) signified 0% Ph metaphase cells in the bone marrow. A major molecular response (MMR) was indicated by a BCR::$ABL1^{IS}$ ≤0.1%, whereas a deep molecular response (DMR) was defined by a BCR::$ABL1^{IS}$ ≤0.01%.

Adverse Events

Hematological and biochemical tests were consistently administered at each follow-up appointment. We recorded AEs, including hematological reactions such as leukopenia or neutropenia, anemia, and thrombocytopenia, in addition to PE, pulmonary hypertension, gastrointestinal reactions (eg, nausea, vomiting, constipation, diarrhea), fatigue, periorbital and limb edema, rash, musculoskeletal pain, liver and kidney function, and conjunctival hemorrhages, and so on. Pleural effusion related to dasatinib therapy was diagnosed through chest computed tomography scan and thoracic ultrasound. The classification and grading of these AEs followed the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

Categorical variables are represented by frequency and percentage. Continuous data obeying normal distribution is presented as the mean accompanied by the standard deviation. If not, the median and interquartile range (IQR) are used as descriptors. The receiver operating characteristic (ROC) curves serve to determine the most suitable cut-off values. Comparison of categorical variables was conducted employing either $\chi 2$ or Fisher's exact test, while the evaluation of continuous variables utilized the Kruskal–Wallis test. Survival probabilities were estimated via the Kaplan–Meier method and Log rank tests. 50 mg and 100 mg daily groups were pooled for concentration

comparisons due to sample size limitations. To minimize confounding by treatment resistance, efficacy assessments (molecular response vs concentration) focused on first-line patients without dose stratification. Similarly, PE analyses evaluated concentration-dependent associations. IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) served for all statistical analyses. Significance was denoted by a p-value <0.05.

Results

Patient Characteristics

Throughout the study period, our hospital provided treatment for a total of 300 CML patients. The exclusion criteria encompassed 11 patients initially diagnosed with either accelerated or blastic phase, 48 patients unable to meet the blood collection time, 84 subjects with incomplete data, and 45 patients lost to follow-up. Consequently, the final study sample included 112 patients, with 73 (65.2%) being male. Demographic data and clinical information are shown in Table 1. The median age at diagnosis stood at 40 years, ranging from 18 to 72 years. The median duration of TKIs treatment spanned 44.4 months (IQR: 27.4–80.2 months). Hypertension and diabetes were the most prevalent pre-existing conditions, amounting to 6.3% (N = 7) and 4.5% (N = 5) respectively. Regarding the EUTOS long-term survival score, 48.2% of patients had a low score, 24.1% had intermediate, 0.9% had high, and in 26.8% the score was unknown. Fifty-three (47.3%) received dasatinib as a first-line TKI, with 47 (42.0%) and 12 (10.7%) receiving it as second and third-line TKIs, respectively. Within the cohort treated with dasatinib as a first-line therapy, 22 were administered a 50 mg dose, while 31 received a 100 mg dose. In later-line therapy, 33 patients underwent dose escalation to 100 mg daily, and 27 maintained 50 mg daily.

Relationship Between Dasatinib Concentration and Clinical Response

A total of 66 and 62 valid dasatinib concentration measurements were obtained for dasatinib at the 50 mg and 100 mg daily, respectively, in addition to comparing the concentrations of the branded drug against its generic counterpart (Table 2). The patients on a daily regimen of 50 mg exhibited C_{min} and C_{max} of 1.63 ± 0.94 ng/mL and 69.93 ± 35.57 ng/mL, respectively. For those administered 100 mg daily, the C_{min} and C_{max} were determined as 3.08 ± 1.48 ng/mL and 129.39 ± 55.59 ng/mL, respectively. Our analysis indicated no significant disparities between the concentrations of the branded and generic of dasatinib. In the 50 mg group, the C_{min} was 1.44 ± 0.99 ng/mL for the branded form versus 1.50 ± 0.94 ng/mL for the generic, while the C_{max} was 67.60 ± 34.85 ng/mL versus 70.94 ± 30.62 ng/mL (P = 0.84). Similarly, in the 100 mg group, the C_{min} for the branded was 3.04 ± 1.39 ng/mL against 3.55 ± 1.73 ng/mL for the generic, and the respective C_{max} values were 133.5 ± 55.36 ng/mL versus 137.13 ± 65.80 ng/mL (P = 0.92).

The relationship between dasatinib concentration and clinical response was analyzed for first-line treatment. Demographic and clinical characteristics of patients with first-line treatment with dasatinib are presented in Table S1. There were no significant differences in demographic and clinical characteristics between 100 mg and 50 mg daily groups. Based on their clinical responses, patients were classified into one of two groups: MMR and non-MMR groups; DMR and non-DMR groups. For dasatinib first-line therapy, the C_{max} in MMR and non-MMR, DMR and non-DMR groups are shown in Table 3. Our results indicated that the MMR and DMR groups demonstrated higher C_{max} in comparison to the non-MMR and non-DMR groups (MMR: 103.8 ± 54.0 ng/mL versus 48.6 ± 13.9 ng/mL, P < 0.001; DMR: 112.7 ± 57.6ng/mL versus 66.2 ± 36.1 ng/mL, P = 0.001). For MMR, the optimum cut-off value was determined as C_{max} > 51.85 ng/mL, with an area under the curve (AUC)=0.85 (95% CI: 0.75–0.96); sensitivity of 80.0%, and specificity of 84.0%; as shown in Figure S1A. For DMR, the optimal cut-off value was found to be C_{max} > 112.5 ng/mL with AUC = 0.76 (95% CI: 0.63–0.89); sensitivity of 92.8%, and specificity of 52.0%; (Figure S1B). We then divided the C_{max} into two groups based on cutoff value: >51.85 ng/mL and ≤51.85 ng/mL, and analyzed the cumulative incidence of MMR. The results indicated that the cumulative incidence of MMR was significantly higher in the >51.85 ng/mL group than in the ≤51.85 ng/mL group (P < 0.001, Figure 1).

Table 1 Demographic and Clinical Characteristics of Patients with Chronic Myeloid Leukemia

Variables	Number. of Patients (N=112)
Sex (male), n (%)	73 (65.2)
Age at diagnosis (years), median (range)	40 (18–72)
TKIs therapy duration (months), median (IQR)	44.4 (27.4–80.2)
Comorbidity, n (%)	
Hypertension	7 (6.3)
Diabetes	5 (4.5)
Coronary heart disease	3 (2.7)
Hepatitis B	3 (2.7)
Others	6 (5.4)
Leukocyte counts at diagnosis[a], 10^9/L	
Median	104.2
Range	40.2–652.6
Platelet counts at diagnosis, 10^9/L	
Median	430.5
Range	92.0–1120.0
Hemoglobin at diagnosis, g/L	
Median	112.0
Range	60.0–265.0
BCR::ABL1/ABL1 ratio at diagnosis, %	
Median	72.7
Range	6.3–416.6
Sokal score, n (%)	
Low	44 (39.3)
Intermediate	32 (28.6)
High	6 (5.4)
Unknown	30 (26.8)
ELTS score, n (%)	
Low	54 (48.2)
Intermediate	27 (24.1)
High	1 (0.9)
Unknown	30 (26.8)
First-line TKIs treatment, n (%)	
Imatinib	50 (44.6)
Dasatinib	53 (47.3)
Nilotinib	4 (3.6)
Flumatinib	5 (6.3)
Line of TKIs, n (%)	
1st line	49 (43.8)
2nd line	41 (36.6)
3rd line	19 (17.0)
Successive line	3 (2.7)
Current TKIs treatment, n (%)	
Dasatinib	100 (89.3)
Nilotinib	1 (0.9)
Flumatinib	10 (8.9)
Clinical trials	1 (0.9)

Notes: a: We obtained data on leukocyte counts, platelet counts, hemoglobin, and BCR::ABL1/ABL1 ratio at diagnosis from 82 CML patients.

Abbreviations: TKI, tyrosine kinase inhibitor; IQR, interquartile range; ELTS score, EUTOS long-term survival score.

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Table 2 Dasatinib Concentrations

	C_{min} (ng/mL)	C_{max} (ng/mL)	P. value
50 mg daily (N=66)	1.63±0.94	69.93±35.57	–
100 mg daily (N=62)	3.08±1.48	129.39±55.59	
Branded 50 mg (N=16)	1.44±0.99	67.60±34.85	0.84
Generic 50 mg (N=50)	1.50±0.94	70.94±30.62	
Branded 100 mg (N=10)	3.04±1.39	133.5±55.36	0.92
Generic 100 mg (N=52)	3.55±1.73	137.13±65.80	

Abbreviations: C_{min}, dasatinib trough concentration; C_{max}, dasatinib peak concentration.

Table 3 The Relationship Between Peak Concentration of Dasatinib and Clinical Response in First-Line Therapy

	C_{max} (ng/mL)	P. value
Non-MMR (N=15)	48.6±13.9	<0.001
MMR (N=38)	103.8±54.0	
Non-DMR (N=28)	66.2±36.1	0.001
DMR (N=25)	112.7±57.6	

Abbreviations: C_{max}, dasatinib peak concentration; MMR, major molecular response; DMR, deep molecular response.

Correlation of Dasatinib Trough Concentration with Adverse Events

The most commonly observed AEs related with dasatinib were thrombocytopenia (36.6%), anemia (35.7%), neutropenia (30.4%), PE (24.1%), and rash (23.2%). Moreover, pulmonary arterial hypertension developed in three patients. Anemia (14.3%), neutropenia (9.8%), and thrombocytopenia (6.3%) constituted the highest incidence rates for grade 3–4 AEs (Table S2). In addition, there were no significant differences in AEs between generic and branded dasatinib (Table S3).

The study explored the correlation between C_{min} and the incidence rate of PE. Among the 27 patients who experienced PE, 25 belonged to the 100 mg dosage group, and 2 were from the 50 mg group. The result suggested

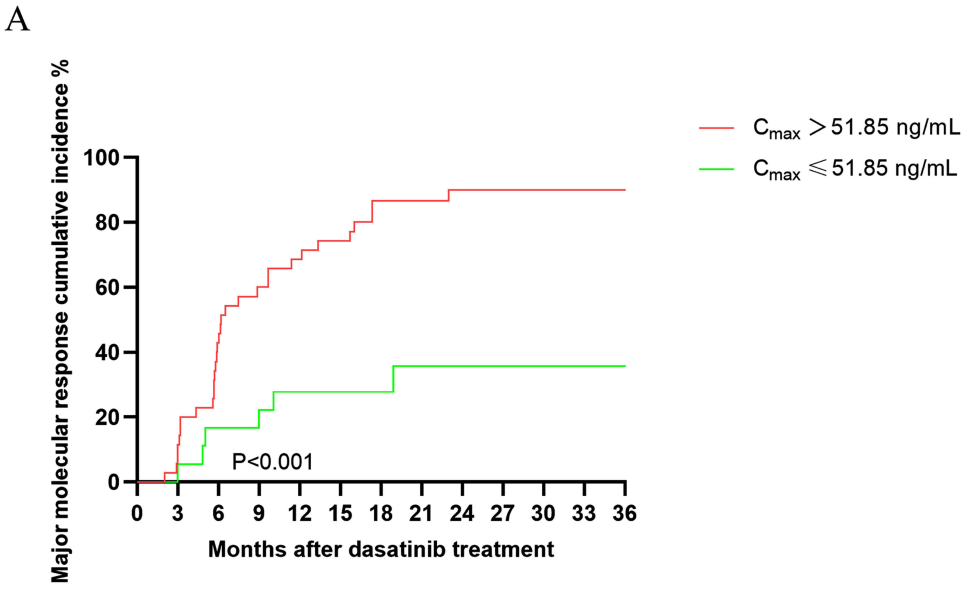

Figure 1 Cumulative major molecular response based on the peak concentration of dasatinib.

a significantly higher C_{min} in patients who encountered PE (4.14 ± 1.19 ng/mL vs 1.89 ± 1.01 ng/mL; P < 0.001, Figure S2A). ROC analysis demonstrated the discriminatory capacity of the C_{min} for PE occurrence. The AUC was estimated at 0.92 (95% CI: 0.87–0.97), endorsing a sensitivity of 96.3% and specificity of 77.6% at a C_{min} threshold of 2.48 ng/mL for PE (Figure S2B). Subsequently, we dichotomized the C_{min} into two groups using this cutoff value: >2.48 ng/mL and ≤2.48 ng/mL. The cumulative incidence of PE was analyzed, revealing a significantly higher incidence in the >2.48 ng/mL group compared to the ≤2.48 ng/mL group (P < 0.001, Figure 2).

The relationship between C_{min} and other AEs is shown in Table S4. A strong association was found between C_{min} and facial and limb edema (P = 0.006), and pigmentation (P = 0.001). The AUC was 0.74 (95% CI: 0.60–0.87) for edema, with a sensitivity of 84.6% and specificity of 61.6% at a threshold of 2.2 ng/mL. For pigmentation, the AUC was 0.76 (95% CI: 0.66–0.87) indicating sensitivity of 70.6% and specificity of 71.6% at a C_{min} of 2.8 ng/mL (Figure S3).

Correlation of Dasatinib Trough Concentration with Age

We also examined the correlation between the incidence rate of PE and patient age (Table S5). The result indicated that patients who experienced PE were significantly older than those who did not (50.8 ± 9.3 years vs 44.9 ± 14.6 years, P = 0.03). Subsequently, we categorized the ages of patients into three groups, based on quartile ranges: <36 years, 36–55 years, and >55 years. We found that patients aged >55 years had a higher PE incidence compared to the other two age categories (36.4% vs 27.5% vs 3.6%; P = 0.01). In addition, we investigated the relationship between dasatinib concentration and patient age (Table S6). The findings revealed that irrespective of whether they treat with the 50 mg or 100 mg dosage group, patients older than 55 years exhibited both higher C_{min} (50 mg: 1.65 ± 2.22 ng/mL vs 1.50 ± 0.73 ng/mL vs 1.26 ± 0.98 ng/mL; P = 0.03; 100 mg: 3.74 ± 1.95 ng/mL vs 3.26 ± 2.48 ng/mL vs 3.09 ± 1.75 ng/mL, P = 0.02) and C_{max} (50 mg: 110.25 ± 16.61 ng/mL vs 76.8 ± 28.76 ng/mL vs 60.24 ± 27.47 ng/mL; P = 0.01; 100 mg: 237.0 ± 93.34 ng/mL vs 164.0 ± 49.0 ng/mL vs 105.97 ± 38.62 ng/mL, P = 0.02) when compared to the other age groups.

Low-Dose Therapy

A total of 48 patients received low-dose dasatinib regimens, with 22 administered as first-line therapy, 21 as second-line, and 5 as third-line treatment. For those on a 50 mg initial regimen (N = 22), the median time to reach a CCyR was 3.2 months, and achieving an MMR took a median of 7.1 months. Except for one patient who switched to flumatinib due to non-responsive treatment, all others maintained their 50 mg daily dosage. From a pharmacokinetics standpoint, patients receiving a 100 mg dosage exhibited C_{min} and C_{max} of 2.54 ng/mL (range: 1.63–5.42 ng/mL), and 152.0 ng/mL (range: 39.1–204 ng/mL), respectively. Comparatively, those prescribed 50 mg daily had C_{min} and C_{max} of 1.24 ng/mL (range:

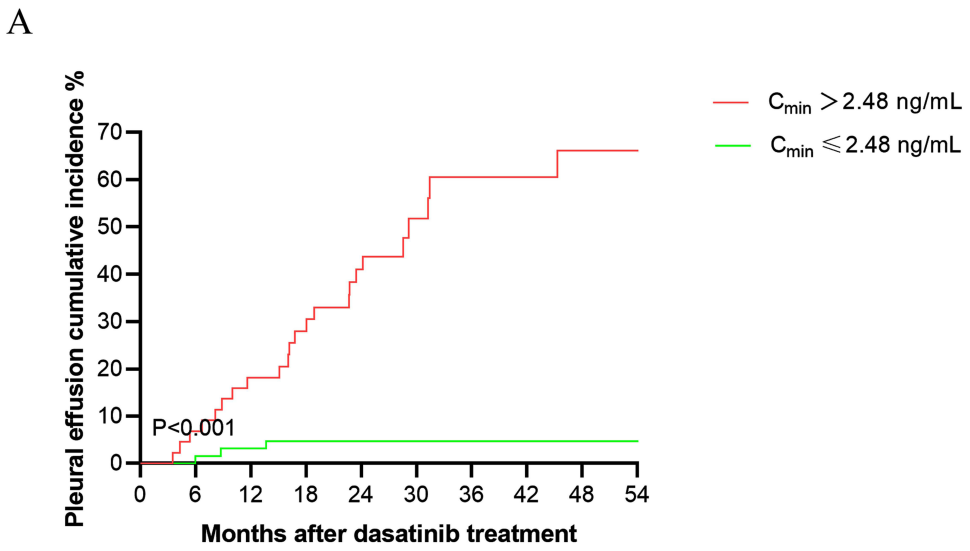

Figure 2 Cumulative incidence of pleural effusion based on the trough concentration of dasatinib.

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0.5–3.5 ng/mL), and 55.2 ng/mL (range: 30.9–139 ng/mL), respectively. These results suggest that a 50 mg daily could yield the concentration range necessary for MMR achievement. Among the 31 patients initially given a 100 mg dasatinib dosage, 22 subsequently reduced their dosage to 50 mg. Notably, these dosage adjustments were executed based on dasatinib concentration and clinical conditions. All these patients have currently maintained a DMR, with 7 further reducing their dosage to 50 mg every other day (qod).

It is important to highlight that in subsequent-line treatments with dasatinib, we recommended a daily dose of 100 mg for patients demonstrating treatment failure to preceding TKIs. Conversely, patients manifesting warning or optimal responses were prescribed a daily dosage of 50 mg, all of whom achieved a DMR. For second-line treatment, the C_{max} was 129.6 ng/mL (range: 17.6–303 ng/mL) and C_{min} was 3.61 ng/mL (range: 0.73–6.41 ng/mL) for patients treated with a 100 mg dosage (N = 26), and 72.5 ng/mL (range: 14.23–227 ng/mL) and C_{min} was 1.37 ng/mL (range: 0.28–3.75 ng/mL) for those administered a 50 mg dose (N = 21). For third-line therapy, the corresponding C_{max} for patients receiving 100 mg (N = 7) and 50 mg doses (N = 5) were 98.3 ng/mL (range: 74.5–145 ng/mL) and 63.9 ng/mL (range: 29.7–111 ng/mL). The corresponding C_{min} for patients receiving 100 mg (N = 7) and 50 mg doses (N = 5) were 3.01 ng/mL (range: 1.94–6.37 ng/mL) and 1.61 ng/mL (range: 0.23–3.20 ng/mL), respectively (Table S7).

Discussion

A growing number of patients with CML are actively seeking dose optimization and personalized treatment. Recent studies suggest that the standardized starting dosage of 100 mg daily dasatinib may not be optimal for all patients with CP-CML.[18,19] Although a reduction in dosage (such as 50 mg daily) has been proposed, there is a noticeable dearth of references to guide the individualization of medication for patients. In this study, our objective was to investigate the use of TDM as a strategy for dasatinib dose optimization in patients with CML.

In vitro studies have suggested that a transient, potent inhibition (>50 ng/mL) is adequate to commit CML cells to apoptosis.[20,21] It is widely accepted that maintaining a relatively high C_{max} is crucial for ensuring clinical effectiveness and mitigating the risk of dasatinib resistance.[22] Our study revealed significant interindividual variability in dasatinib blood concentrations. Patients administered 100 mg demonstrated significantly higher concentrations than those given 50 mg, with no notable difference in concentration between branded and generic drugs. Further analysis revealed a strong correlation between C_{max} and clinical response. Patients with a C_{max} >51.85 ng/mL were more likely to achieve MMR, while those with C_{max} >112.5 ng/mL were more likely to achieve a DMR. It is noteworthy that the majority of patients receiving 50 mg daily achieved a C_{max} >50 ng/mL, which provides more basis for the first-line 50 mg daily treatment regimen.

Moreover, we successfully guided a reduction in dosage from 100 mg to either 50 mg daily or 50 mg qod for 22 patients receiving dasatinib as first-line treatment. This decision was based upon comprehensive evaluations of their blood drug concentration and clinical responses. In the context of subsequent-line treatments with dasatinib, we recommend 100 mg daily for patients who exhibit treatment failure to preceding TKIs. Conversely, we advise 50 mg daily for patients demonstrating warning or optimal responses. Remarkably, all patients administered 50 mg dasatinib as a later-line therapy achieved a DMR.

The connection between the C_{min} of dasatinib and the incidence of PE in patients is broadly established, with evidence suggesting that maintaining a relatively low C_{min} level can mitigate the risk of PE. However, the optimal target range for dasatinib C_{min} remains controversial, with studies proposing divergent thresholds based on varying clinical endpoints. Wang et al[7] and Verheijen et al[8] both reported a steady-state C_{min} of ~2.61 ng/mL at the 100 mg dose. While Wang et al identified C_{min} as a significant predictor of PE, with a 1.22-fold increased hazard per 1 ng/mL rise, Verheijen et al suggested this value as a pragmatic target in the absence of formal TDM. Conversely, Yu et al[23] advocated for a stricter upper threshold (<2.5 ng/mL) to avoid dose interruptions, and Mizuta et al[24] reported no significant difference in PE rates between high (≥1.4 ng/mL) and low (<1.4 ng/mL) C_{min} groups, despite higher C_{min} correlating with dose reductions. Notably, the OPTIM Phase II study introduced a distinct approach, demonstrating that proactive TDM to maintain C_{min} ≥1.5 ng/mL (≈3 nmol/L) reduced long-term PE incidence without compromising molecular responses.[25] These conflicting recommendations—ranging from lower thresholds for tolerability (1.4–1.5 ng/mL) to higher targets for efficacy (2.5–2.6 ng/mL)—highlight the challenges in defining a universal range. Furthermore, age was a major risk

factor for PE, and it was found that this effect was driven by PK parameters.[26] Our study found that C_{min} >2.48 ng/mL were closely linked to the occurrence of PE. We also observed higher C_{min} and C_{max} in older patients, regardless of whether they received a 50 mg or 100 mg dosage. Our data supports that a daily 50 mg dosage is feasible and safe for Chinese CML patients. Furthermore, elderly patients seemingly have a narrower therapeutic window; thus, a 50 mg daily dosage may be more appropriate for them, but warranting more intensive monitoring.

The results may advocate for integrating TDM into clinical decision pathways for CML-CP patients receiving dasatinib. The proposed suggestions could include: ①baseline TDM assessment (C_{max}/C_{min}) prior to dose reduction; ② dose escalation to 100 mg if C_{max} <51.85 ng/mL; ③ dose de-escalation to 50 mg if C_{max} exceeds safety thresholds or C_{min} >2.48 ng/mL, particularly in elderly patients with elevated drug exposure. Our findings identify a balanced threshold that optimizes efficacy while minimizing toxicity, thereby advancing the rationale for personalized TDM-guided dosing in clinical practice.

Our study has several limitations that warrant discussion. Primarily, the single-center retrospective design and modest sample size inherently restrict the generalizability of findings, compounded by limited ethnic diversity within the cohort. These methodological constraints necessitate cautious interpretation when extrapolating results to broader populations, particularly those from distinct geographic/ancestral backgrounds. Second, the inherent pharmacokinetic variability of dasatinib, manifested through temporal concentration fluctuations and delayed plasma sampling intervals, underscores the need for validation through large-scale multicenter randomized controlled trials employing standardized therapeutic drug monitoring protocols. In addition, routine TDM implementation requires cost–benefit analysis relative to empirical dose reduction strategies, especially in resource-limited settings. Furthermore, medication adherence was operationalized through self-reported compliance rather than objective measures, which may introduce misclassification bias in exposure assessment.

In conclusion, the C_{max} of dasatinib has been found to align with clinical response, while the C_{min} appears closely associated with PE. This suggests that TDM-based dose optimization could yield beneficial clinical outcomes for patients with CML-CP. Furthermore, from the perspective of blood drug concentration, our findings provides more evidence for the first-line treatment regimen of 50 mg daily.

Data Sharing Statement

The original contributions presented in the study are included in the article.

Ethics Approval and Consent to Participate

This study has been approved by the institutional ethics committee of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) ([2021] 0784). Written informed consent was obtained from all the participants prior to the study.

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Disclosure

The authors report no conflicts of interest in this work.

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