

## **Relationship between an optimal dose of imatinib, body surface area, and trough drug levels in patients with chronic myeloid leukemia**

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**Abstract (194 words)**

The standard dose of imatinib for treatment of chronic-phase chronic myeloid leukemia (CML) is 400 mg/day. Some patients receive reduced doses of imatinib because of serious adverse effects. Recently, the effective plasma threshold for trough imatinib levels was demonstrated to be 1,002 ng/ml. In this study, we evaluated the association of an imatinib dose with trough plasma concentrations and clinical outcomes in 31 patients with chronic-phase CML who were treated at Kumamoto University Hospital. Twenty-seven patients were optimally treated with various doses of imatinib. The mean ( $\pm$ SD) trough plasma concentrations of imatinib were  $1.40 \pm 0.57 \mu\text{g/ml}$  in 13 patients receiving 400 mg/day and  $1.15 \pm 0.44 \mu\text{g/ml}$  in 9 patients receiving 300 mg/day as an optimal dose. Mean trough levels of the two groups were not significantly different and exceeded the effective plasma threshold. Body surface area (BSA) was significantly smaller in patients receiving the reduced dose compared with those receiving the standard dose ( $p=0.001$ ). The optimal imatinib dose was associated with age and gender as well as BSA. A reduced dose of 300 mg/day of imatinib may be sufficient for treatment of CML patients with smaller body size, particularly when intolerability arises.

Keywords: Chronic myeloid leukemia, imatinib, optimal dose, body surface area

## **1 Introduction**

Imatinib mesylate, an inhibitor specific for the *TK* domain in the Abelson proto-oncogene, c-kit, and platelet-derived growth factor receptor, has been shown to be highly effective in the treatment of patients with chronic myeloid leukemia (CML) and gastrointestinal stromal tumors [1-4]. Based on the IRIS study [2, 3], the established standard dose of imatinib is 400 mg/day for patients with chronic-phase CML. This dose is well tolerated by most patients, and plasma trough levels are dose-proportional for the dose range of 25 to 1,000 mg/day [5]. The relationship between pharmacokinetics and pharmacodynamics of imatinib at steady state indicates that clinical response is highly dependent on the administered dose for patients with CML, and that a dose of 400 mg/day or higher is required for maximal clinical outcomes [1, 5, 6]. Recently, Picard et al demonstrated that trough imatinib plasma levels at steady-state must exceed 1,002 ng/ml to obtain the best sensitivity in CML patients, and that the plasma imatinib concentrations are associated with clinical response [7]. Similarly, Larson et al reported on the pharmacokinetics of imatinib and their correlation with clinical response during 5 years of follow-up in the IRIS study [8]. These authors indicated that maintaining plasma trough levels at or above 1,002 ng/ml may be important for achieving a complete cytogenetic response (CCR) and a major molecular response (MMR).

The recommended dose of 400 mg/day imatinib sometimes causes severe adverse effects such as myelo-suppression, edema, and skin rash, which in turn may lead to poor compliance, premature cessation of treatment, and failure of therapy. To avoid these unfavorable clinical situations, the daily dose of imatinib is often reduced from 400 to 200-300 mg/day in clinical practice [9-11], although maintaining a low dose of imatinib is not generally recommended. Recently, Ohnishi et al suggested that a reduced dose of 300 mg/day imatinib might be enough to achieve a CCR in some Japanese patients, and a weak inverse-correlation was observed between imatinib trough levels and body weight [12]. However, it is not known whether the plasma concentrations of imatinib reach the effective level (1,002 ng/ml) in such patients having a favorable response to a reduced dose of imatinib. Indeed, there are little data on the pharmacokinetics and pharmacodynamics of patients given a reduced dose of imatinib. To clarify the relationship of the optimal dose of imatinib with trough levels of imatinib at steady state, we measured plasma concentrations of imatinib in chronic-phase CML patients responding to a reduced dose of 300 mg/day as well as to a standard dose of 400 mg/day and analyzed differences in patient characteristics between these two patient groups.

## **2 Materials and Methods**

### **2.1 Patients and treatment**

Plasma concentrations of imatinib at steady state (on day 30 of treatment or later) were assessed in 31 patients with chronic-phase CML who were followed up at Kumamoto University Hospital during 2003 to 2007. All patients were initiated with the standard-dose of 400 mg/day imatinib. In case of severe adverse drug events (Grade 2 or more on the Common Toxicity Criteria of the National Cancer Institute), imatinib was reduced to 100 to 300 mg/day or temporarily discontinued until adverse events were ceased, and resumed from a low dose and increased gradually up to a tolerable dose. When adverse events ( $\geq$  Grade 2) repeated, low dose imatinib (200 or 300 mg/day) was continued with careful monitoring of imatinib response. In contrast, imatinib dose was escalated up to 800 mg/day if an optimal response (CCR) was not achieved after treatment with 400 mg/day imatinib for one year. Dose of imatinib that could achieve and maintain a CCR during the observation period was defined as “an optimal dose” in this study. Approval from the ethics committee in Kumamoto University Hospital was obtained, and all patients provided informed consent to participate in this study, which was performed in accordance with the Declaration of Helsinki. Cytogenetic responses to imatinib were assessed using a conventional cytogenetic analysis of bone marrow metaphases. CCR was defined as 0% of Philadelphia chromosome-positive cells in bone marrow aspirate. To assess molecular responses, total RNA was extracted from peripheral blood cells or bone marrow cells, and *BCR-ABL* transcript levels were quantified using

real-time quantitative PCR. Three or more log reduction in the transcript levels was determined to be a major molecular response (MMR).

## 2.2 Pharmacokinetic sample analysis

Blood samples were collected at steady state (day 30 of treatment or later) prior to the morning dose (trough plasma levels). Plasma levels of imatinib were determined using high performance liquid chromatography as described previously [13]. Briefly, EDTA-containing blood samples (5 ml) were collected from patients at steady state and were immediately centrifuged (1500 *g*, 5 min at 4°C) to obtain the plasma fraction. The separated plasma was stored at -80°C until measurement of plasma imatinib concentrations.

## 2.3 Statistical analysis

Data on trough plasma levels of imatinib are presented as mean values with 95% confidence intervals (CI). The *t* test was used to determine differences in imatinib trough levels between different dose groups. Fisher's exact test was used to evaluate the association of an optimal dose at steady state with gender, age at starting treatment (below or above the median value of 53 years), body surface area (BSA; below or above the median value of 1.68 m<sup>2</sup>), and prior interferon (IFN) treatment. JMP ver. 7 (SAS Institute Inc., Cary, NC) was used for all statistical analyses. A *p* value <0.05 was considered statistically significant.

### 3 Results

#### 3.1 Patient characteristics

The characteristics of the 31 patients are shown in Table 1. The median age was 49 years (range, 24-80), with 18 males and 13 females. All patients showed adequate hepatic and renal functions: mean values (95% CIs) of ALT, AST, total bilirubin, BUN, serum creatinine, and serum albumin were 23 (20-26) IU/L, 24 (18-30) IU/L, 0.5 (0.5-0.6) mg/dL, 14.0 (12.6-15.4) mg/dL, 0.82 (0.74-0.91) mg/dL and 4.4 (4.3-4.5) g/dL, respectively. Each of the patients started with the standard recommended daily dose (400 mg) of imatinib. However, the daily dose was subsequently modified according to individual requirements. The main reasons for dose reduction were cytopenia, gastrointestinal symptoms, such as diarrhea and nausea, or development of a skin rash (Table 1). Of the 31 patients, 4 patients discontinued imatinib: 2 patients could not tolerate even 200 mg/day imatinib due to severe cytopenia; one patient developed a concomitant unrelated disease (lung cancer); one patient showed imatinib-resistance and was enrolled to a clinical trial for a second-generation tyrosine kinase inhibitor.

#### 3.2 Imatinib dose and clinical outcome

Twenty-seven patients tolerated the drug well and showed clinical benefit: 13 patients were maintained with imatinib at a standard dose of 400 mg/day, 9 patients were treated at a reduced dose of 300 mg/day, and 5 patients received

a high dose of 500 or 600 mg/day. All of 27 patients achieved a CCR and sustained this favorable response during the follow-up period, indicating that the dosage of imatinib was considered optimal for individual patients. 16 (59%) of 27 patients with CCR achieved a MMR, but there was no significant difference in MMR rates between patients receiving 300 mg/day imatinib and those receiving 400 mg/day imatinib. None of the patients receiving 300 mg/day imatinib showed signs of disease progression.

### 3.3 Trough plasma concentrations of imatinib at different doses

The relationship between dose and plasma trough level at steady state is shown in Figure 1. The increase in mean plasma level was proportional to the dose of imatinib. Mean ( $\pm$  SD) trough plasma levels of imatinib at a standard dose of 400 mg/day were  $1.40 \pm 0.57 \mu\text{g/ml}$  ( $n=13$ , 95% CI 1.33-1.47  $\mu\text{g/ml}$ ). Trough levels at a reduced dose of 300 mg/day were  $1.15 \pm 0.44 \mu\text{g/ml}$  ( $n=9$ , 95% CI 1.05-1.25  $\mu\text{g/ml}$ ). There was no significant difference in plasma trough levels between patients receiving 300 mg/day and 400 mg/day ( $p=0.26$ ). Both mean plasma concentrations exceeded the effective plasma threshold for trough imatinib levels (1,002 ng/ml), which was proposed by Picard et al to give a favorable response [7]. In contrast, a dose of 200 mg/day did not reach the effective plasma concentration. Five patients achieved a CCR at a dose of 500 or 600 mg/day without developing serious adverse effects. There was no relationship between trough plasma levels and severity of adverse events (data not shown:



see supplement Figure). Interestingly, mean trough levels of imatinib tended to be higher in patients with MMR ( $1.642 \pm 0.709 \mu\text{g/mL}$ ) than those with CCR ( $1.467 \pm 0.494 \mu\text{g/mL}$ ).

### 3.4 Relationship between optimal dose of imatinib and BSA

It is clinically important to clarify the reason why low-dose imatinib was sufficient in a proportion of our patients to reach the effective plasma trough concentration. Recently, a weak correlation between steady-state trough levels of imatinib and BSA was identified and imatinib exposure (area under the curve or plasma concentration) was dose proportional in a subanalysis of the IRIS study [8]. Considering the lower median BSA in the present study (male,  $1.76 \text{ m}^2$ ; female  $1.44 \text{ m}^2$ ) as compared with that in the IRIS study (male,  $2.0$ ; female,  $1.75 \text{ m}^2$ ), the optimal dose of imatinib may be correlated with BSA. Thus we evaluated the relationship of BSA with optimal dose (300 mg/day vs. 400 mg/day) of imatinib. As shown in Figure 2, the median ( $\pm$ SD) BSA of patients receiving 300 mg/day was significantly smaller than that of patients receiving 400 mg/day ( $1.46 \pm 0.16$  vs.  $1.76 \pm 0.15 \text{ m}^2$ ,  $p=0.001$ ). Because older and/or female Japanese individuals generally have a small body size [9], we further evaluated the associations of an optimal dose (300 vs. 400, 500, and 600 mg/day) with age, gender, prior treatment with IFN, and BSA (Table 2). An optimal dose of imatinib was significantly associated with age ( $p=0.009$ ), gender ( $p=0.034$ ), and BSA

( $p=0.004$ ), but not with prior IFN therapy. Thus, the present data suggest that an optimal dose of imatinib can be set lower than the standard dose of 400 mg/day in smaller or older female patients.

## Discussion

The standard 400 mg/day dose of imatinib is well tolerated for chronic-phase CML patients. Despite its favorable efficacy, reduced doses of imatinib are sometimes used because of severe toxicity issues [9]. In fact, 8% of patients received less than 400 mg/day during the 5-year follow-up in the IRIS study [3]. The mean daily dose for **Japanese** patients with early chronic-phase CML was reported to be relatively lower: 300 mg in 27% and 200 mg or lower in 20% [12]. In the present study, 9 (33.3%) out of 27 patients who achieved a CCR had been treated with imatinib at 300 mg/day. Importantly, the mean trough level of imatinib of the patients exceeded the effective plasma threshold (1,002 ng/ml), suggesting that monitoring of imatinib plasma concentrations may be beneficial to predict a clinical outcome when a reduced dose of imatinib is considered in a clinical setting.

The correlation of imatinib dose with trough imatinib concentrations was comparable to the IRIS study [8]; however, the mean ( $\pm$  SD) trough plasma concentration of imatinib at 400 mg/day was much higher in our study ( $1.40 \pm$

0.57  $\mu\text{g/ml}$ ) than in the IRIS study ( $0.98 \pm 0.53 \mu\text{g/ml}$ ). This difference is partly explained by smaller BSA of our cohort as compared with that of the IRIS study, because a weak inverse-correlation was observed between trough concentrations of imatinib and BSA in the large-scale study [8]. Racial disparities of BSA may be related with a disparity in trough concentrations of imatinib between Asian and American or European subjects.

Our study indicated that BSA was significantly lower in patients receiving 300 mg/day imatinib as an effective dose than 400 mg/day. By considering BSA with trough concentrations, a dose of 300 mg/day seems to be enough to obtain the therapeutic efficacy equivalent to the standard dose of 400 mg/day in patients with small body size, because the plasma trough level of imatinib would exceed the therapeutic concentration (1,002 ng/ml). Similar results have been reported from Asian countries: a lower dose of imatinib (200-300 mg/day) led to clinical benefits in five Japanese CML patients with low BSA (median value, 1.46 m<sup>2</sup>) [9]; Korean CML patients with low BSA (median value, 1.55 m<sup>2</sup>) benefited from 300 mg/day imatinib [10]. Taken together, these observations suggest that the standard dose of 400 mg/day imatinib may be too high as an optimal dose for a proportion of patients with chronic phase CML having low BSA and that such patients can be optimally managed with reduces doses of imatinib if the effective imatinib trough levels are sustained. Thus, individualized dose optimization

based on plasma imatinib concentrations is considered a key feature of imatinib therapy in patients with CML, particularly when intolerability arises [14].

We did not evaluate the association between an optimal dose of imatinib with drug-metabolizing enzymes and drug transporter genotypes. Previous reports demonstrated an association between the pharmacokinetics of imatinib and ABC transporters (ABCB1, ABCC1, ABCG2), human organic cation transporter (OCT1), and cytochrome P450 isoenzymes, such as CYP2C9 and CYP3A4/5 [15-18]. The role of the genetic variants and race differences in inter-individual variability in imatinib pharmacokinetics remains controversial, and further investigations are needed to determine the relative role of genetic variation and BSA variability on the optimal dose and pharmacokinetics of imatinib.

In summary, the imatinib dose that could give an optimal response with tolerable adverse effects was significantly associated with BSA, age or gender in our cohort. A reduced dose of 300 mg/day imatinib may be sufficient for the treatment of CML patients with small body size. To avoid insufficient efficacy at reduced doses, monitoring of plasma imatinib levels is recommended. A proposed algorithm for management of CML patients on the basis of therapeutic drug monitoring of imatinib may help to make a proper clinical decision, when imatinib dose modification is required in the clinical setting (Figure 3). Further

studies on a larger cohort of CML patients for a longer follow-up period are needed to confirm the relationship of the optimal dose with BSA and trough plasma concentrations of imatinib.

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## **Titles and legends to figures**

### **Figure 1. Relationship of trough plasma concentrations of imatinib at steady state with administered dose**

Each point represents the mean ( $\pm$  SD) plasma imatinib trough concentration.

### **Figure 2. Comparison of body surface area (BSA) between patients receiving 300 mg/day vs 400 mg/day imatinib as an optimal dose**

Boxes represent the distribution of the 25th and 75th percentiles; lines within boxes represent median values. Bars represent ranges.

### **Figure 3. A proposed model of CML patient management on the basis of therapeutic drug monitoring (TDM) of imatinib**

\*Patients who are unable to maintain the initial dose of 400 mg daily due to persistent adverse effects (usually  $\geq$  Grade 2).

\*\*Number of patients examined in the present study is indicated in parenthesis for reference. One patient discontinued 300 mg imatinib before the sixth month

evaluation for cytogenetic response due to chemotherapy for concomitant lung cancer.

\*\*\* Target Cmin: Target trough concentration of imatinib. 1,002 ng/mL is recommended as target Cmin according to reference no.7 and no.8.

**Table 1. Characteristics of the 31 patients treated with imatinib**

Characteristic	Total	Daily dose of imatinib at steady state (median ± SD)			
		200mg	300mg	400mg	>500mg
Gender (no.)					
Male	18	0	3	10	5
Female	13	2	7	3	1
Body surface area (m <sup>2</sup> )					
Median (male; female)	1.68 (1.76; 1.44)	1.35, 1.58	1.45 ± 0.14	1.76 ± 0.14	1.76 ± 0.18
Range	1.28-2.02				
Age at diagnosis (years)					
Median	49	42, 71	58 ± 10	41 ± 11	41 ± 9
Range	24-80				
Age at starting treatment (years)					
Median	52	42, 75	62 ± 9	46 ± 12	48 ± 8
Range	24-85				
Duration of treatment (months)					
Median	45	16, 30	44 ± 21	52 ± 21	34 ± 20
Range	5-72				
Prior interferon-α treatment (no.)					
Yes (no. of CCR)	16 (7)	1	5 (3)	6 (2)	4 (2)
No	15	1	5	7	2
Response to imatinib					
MMR	16		5	10	1
CCR	11		4	3	4
Resistance <sup>a</sup>	1				1
Intolerance <sup>b</sup>	2	2			
Unable to evaluate <sup>c</sup>	1		1		
Imatinib-related adverse events (no.) <sup>d</sup>					
Edema	15 / 0	0 / 0	4 / 0	8 / 0	3 / 0
Skin rash	10 / 1	1 / 0	2 / 1	4 / 0	3 / 0
Cytopenia	4 / 4	0 / 1	2 / 3	1 / 0	1 / 0
Gastrointestinal	9 / 0	1 / 0	3 / 0	2 / 0	3 / 0
Myalgia or muscle cramp	4 / 0	0 / 0	2 / 0	1 / 0	1 / 0
Renal dysfunction	1 / 0	0 / 0	1 / 0	0 / 0	0 / 0

CCR, complete cytogenetic response; MMR, major molecular response

<sup>a</sup> One patient with no cytogenetic response after 12 months of 800 mg/day imatinib.

<sup>b</sup> Two patients had intolerable side effects despite a reduced imatinib dose of 200 mg/day. These 3 patients (2 with intolerable side effects and 1 with no response) ceased imatinib therapy.

<sup>c</sup> A patient discontinued 300 mg/day imatinib before the sixth month evaluation for cytogenetic response due to chemotherapy for concomitant lung cancer.

<sup>d</sup> Values represent grade 1 or 2 / grade 3 or 4

**Table 2. Correlation of an optimal dose of imatinib with gender, age, body surface area (BSA), and prior interferon (IFN) treatment**

Characteristic	Reduced dose (300 mg/day, n=9)	Standard dose or higher (400 mg/day, n=13; 500 or 600 mg/day, n=5)	<i>P</i> value <sup>a</sup>
<b>Gender</b>			
Male	3	14	
Female	6	4	
% of females	66.7%	22.2%	0.034
<b>Age (years)<sup>b</sup></b>			
≥53	8	6	
<53	1	12	
% of older than 53	88.9%	33.3%	0.009
<b>BSA (m<sup>2</sup>)</b>			
≥1.68	1	13	
<1.68	8	5	
% of less than 1.68	88.9%	27.8%	0.004
<b>Prior IFN therapy</b>			
Yes	5	10	
No	4	8	
% of yes	55.6%	55.6%	0.66

All patients at reduced dose (300 mg/day), standard dose (400 mg/day), and higher dose (500 or 600 mg/day) achieved a CCR or a MMR without developing severe adverse events during treatment with imatinib.

<sup>a</sup>Fisher's exact test was used to evaluate the association of an optimal dose with gender, age, BSA, and prior IFN treatment.

<sup>b</sup>Median age at starting imatinib treatment was 53 years olds.

Figure 1

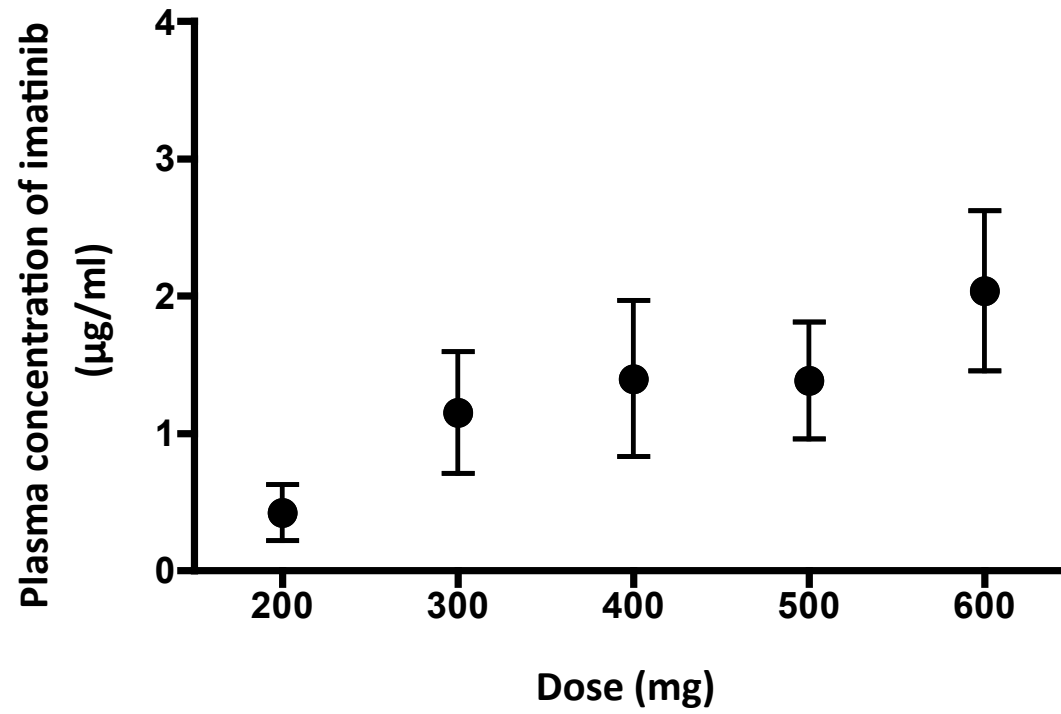


Figure 2

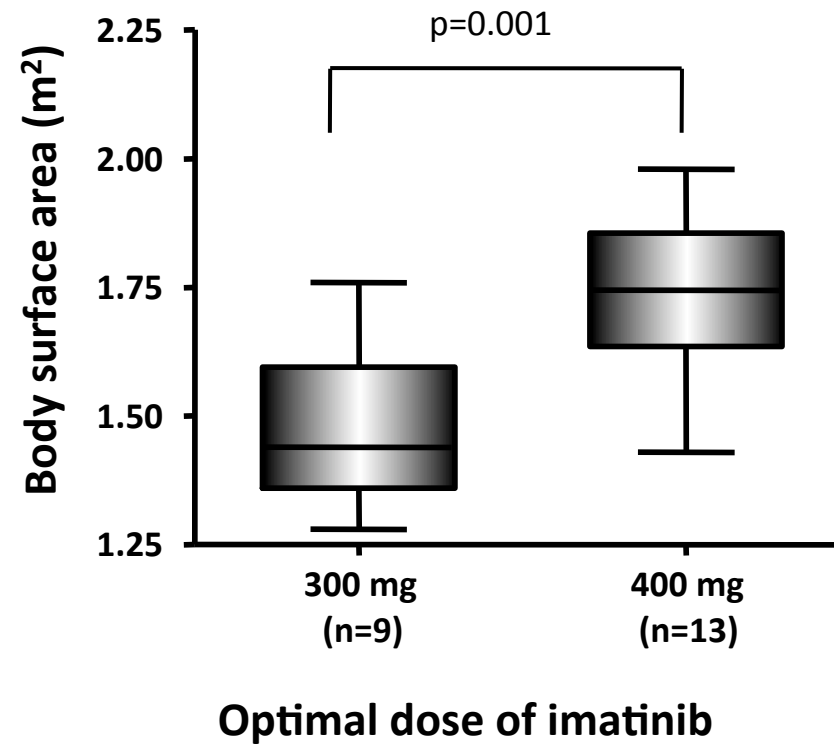
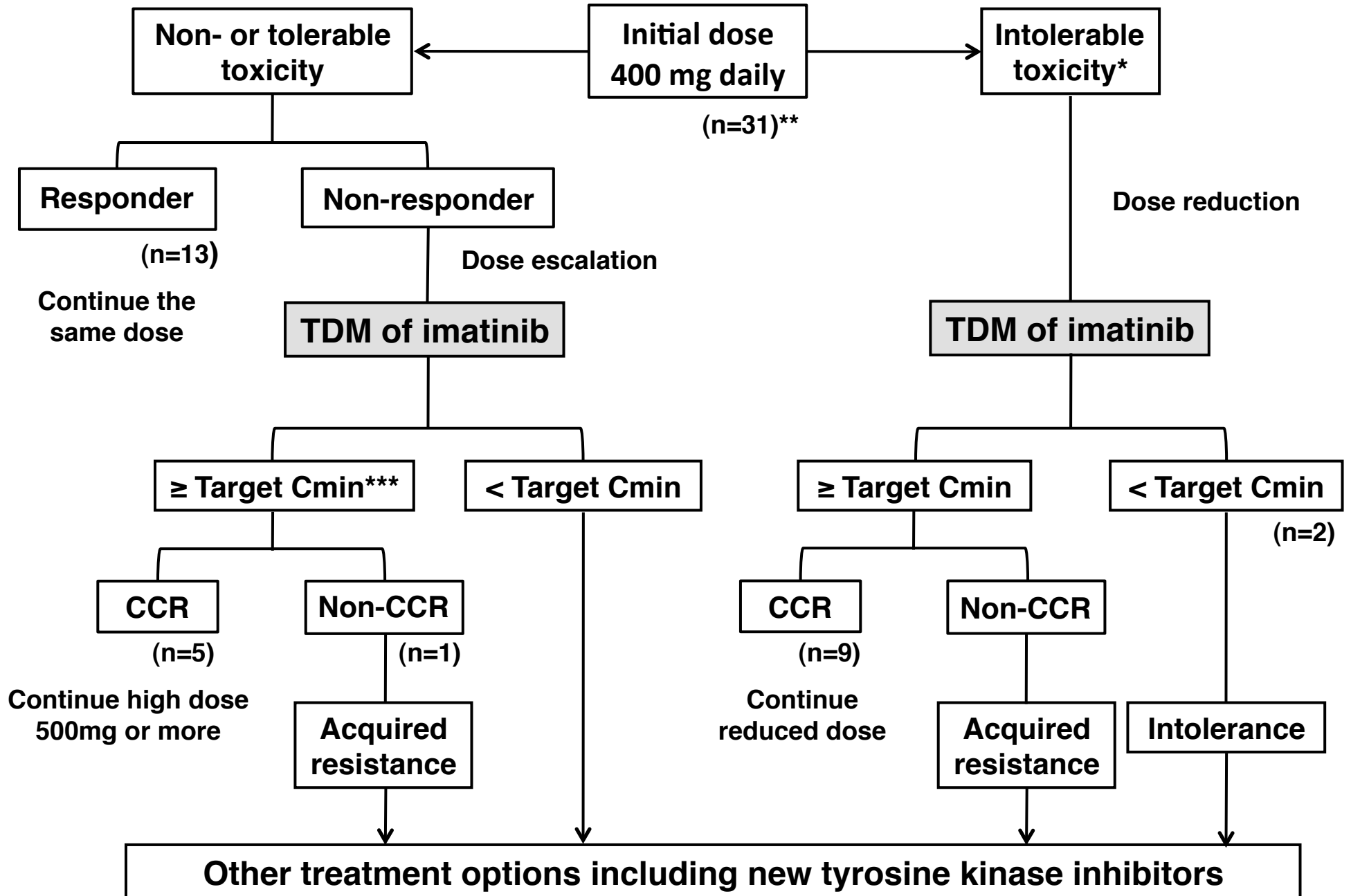


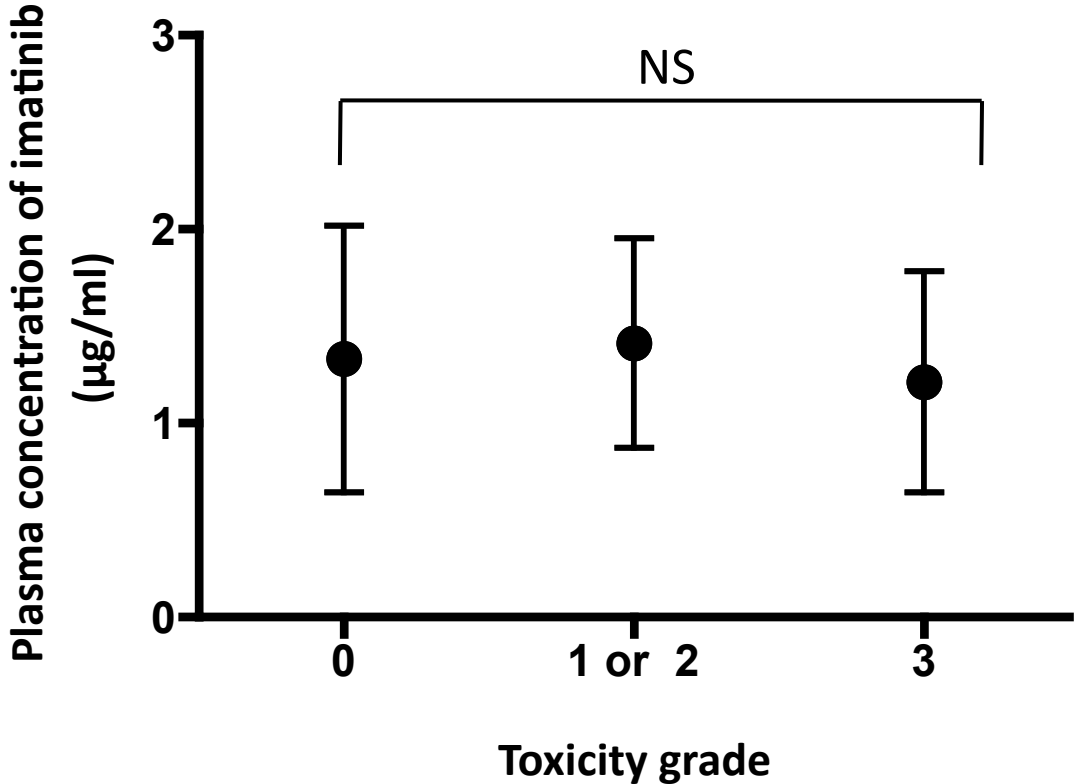


Figure 3



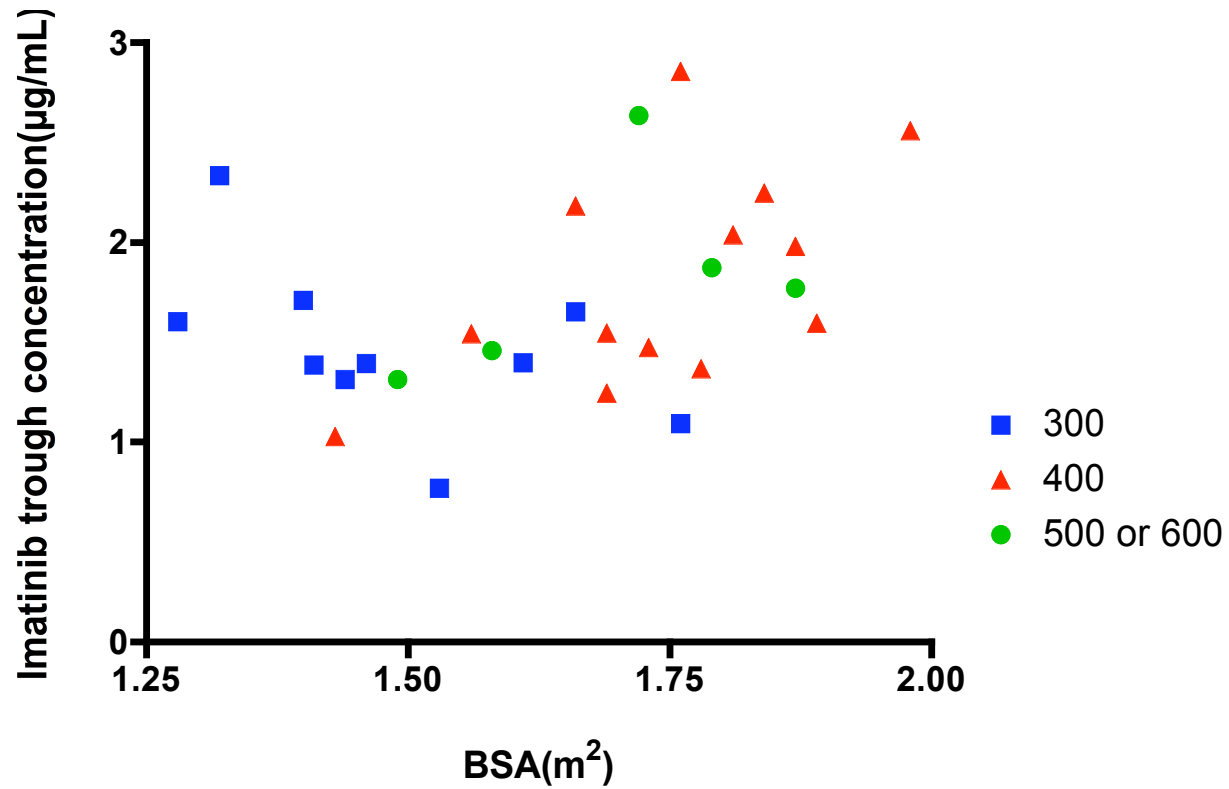
**Supplemental Figure A.**

**Imatinib trough concentrations in CML patients who develop toxicity**



The mean ( $\pm$ SD) plasma imatinib trough concentration was  $1.33 \pm 0.69$  for grade 0,  $1.41 \pm 0.54$  for grade 1 or 2, and  $1.21 \pm 0.57$  for grade 3. There is no correlation between imatinib concentration and toxicity grade. NS: not significant.

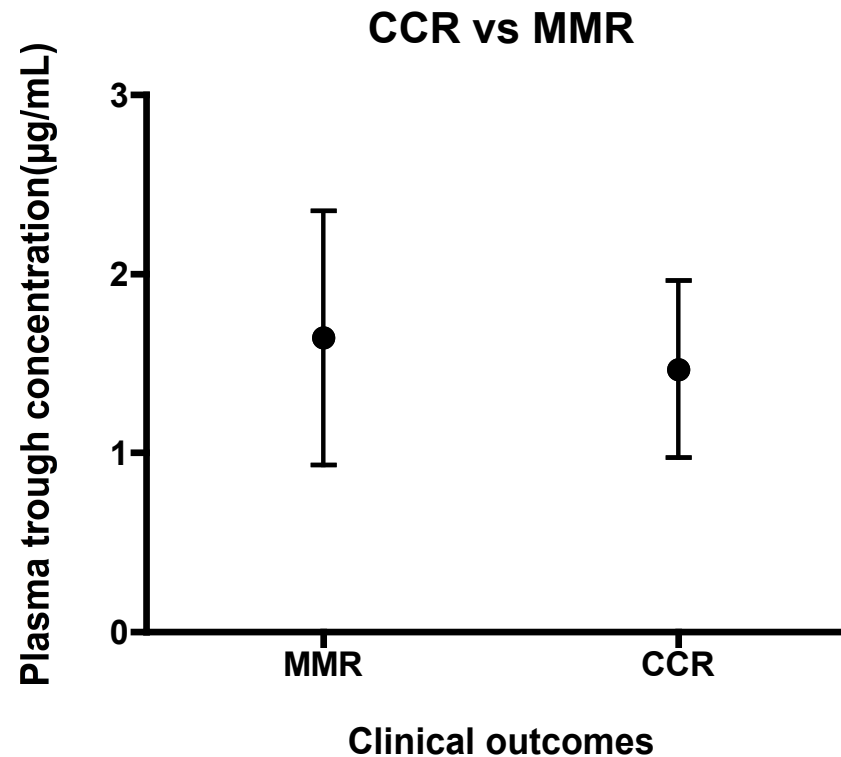
**Supplemental Figure B.**  
**Relationship of imatinib trough levels with BSA**



There is no statistically significant relationship between imatinib trough levels and BSA in each dose group.

## Supplemental Figure C.

Comparison of imatinib trough levels between MMR and no MMR for patients with CCyR



The mean ( $\pm$ SD) plasma imatinib trough concentration:

1.642  $\pm$  0.709  $\mu$ g/mL in patients with CCR who achieved a MMR (n=16, left),

1.467  $\pm$  0.494  $\mu$ g/mL in patients with CCR who did not achieve a MMR (n=11, right).

There is a statistically significant difference between two groups ( $P$  value = 0.0189, Unpaired  $t$  test with Welch's correction).