Utility of Therapeutic Drug Monitoring of Imatinib, Nilotinib, and Dasatinib in Chronic Myeloid Leukemia: A Systematic Review and Meta-analysis

Manuel García-Ferrer, MD[1]; Aneta Wojnicz, MSc PhD[2]; Gina Mejía, MD[2,3]; Dora Koller, MSc[2]; Pablo Zubiaur, MSc[2]; and Francisco Abad-Santos, MD PhD[2,3,4]

[1]Department of Radiology, Hospital Universitario Virgen del Rocío, Seville, Spain; [2]Department of Clinical Pharmacology, Hospital Universitario de La Princesa, Instituto Teófilo Hernando, Facultad de Medicina, Universidad Autónoma de Madrid, Instituto de Investigación Sanitaria La Princesa, Madrid, Spain; [3]UICEC Hospital Universitario de La Princesa, Plataforma Spanish Clinical Research Network, Instituto de Investigación Sanitaria La Princesa, Madrid, Spain; and [4]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Instituto de Salud Carlos III, Madrid, Spain

ABSTRACT

Purpose: This study examined the utility of therapeutic drug monitoring (TDM) of imatinib, nilotinib, and dasatinib in adult patients with chronic-phase chronic myeloid leukemia (CML). TDM in CML entails the measurement of plasma tyrosine kinase inhibitor (TKI) concentration to predict efficacy and tolerability outcomes and to aid in clinical decision making. TDM was to be deemed useful if it could be used for predicting the effectiveness of a drug and/or the occurrence of adverse reactions. It was expected that the findings from the present study would allow for the definition of a therapeutic range of each TKI.

Methods: A systematic review of studies reporting trough TKI levels (C_{min}) and clinical outcomes was performed. We included randomized clinical trials, nonrandomized controlled studies, interrupted time series studies, and case series studies that provided information about plasma levels of imatinib, nilotinib, or dasatinib and relevant clinical end points in adult patients with chronic-phase CML treated with the corresponding TKI as the single antiproliferative therapy. Meta-analyses, Student *t* tests, and receiver operating characteristic analyses were performed to detect mean differences between groups of patients with or without: (1) the achievement of major molecular response and (2) adverse reactions.

Findings: A total of 38 studies (28 for imatinib, 7 for nilotinib, and 3 for dasatinib) were included in the systematic review. TDM was found useful in predicting the efficacy of imatinib, with a C_{min} cutoff value of 1000 ng/mL, consistent with guideline recommendations. We suggest a therapeutic range of imatinib at a C_{min} of 1000–1500 ng/mL because higher concentrations did not increase efficacy. The findings from the rest of the comparisons were inconclusive.

Implications: TDM is useful in predicting the efficacy of imatinib in CML. Further research is needed to determine its validity with nilotinib and dasatinib. (*Clin Ther*. 2019;41:2558–2570) © 2019 Elsevier Inc. All rights reserved.

Keywords: chronic myeloid leukemia, dasatinib, imatinib, nilotinib, therapeutic drug monitoring, tyrosine kinase inhibitor.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm caused by the fusion of the *BCR* gene (chromosome 22) to the *ABL* gene

Accepted for publication October 15, 2019
https://doi.org/10.1016/j.clinthera.2019.10.009
0149-2918/$ - see front matter

(chromosome 9), creating a constitutively active tyrosine kinase that dysregulates myeloid stem cell proliferation.[1] The most common molecular abnormality is the t (9; 22) translocation, which generates the Philadelphia chromosome. Imatinib, a tyrosine kinase inhibitor (TKI), was found effective in the treatment of this condition at the beginning of this century,[2] greatly improving the prognosis when compared to the then-standard interferon-based therapy.[3,4] Nilotinib and dasatinib followed as second-generation TKIs, improving efficacy in imatinib-resistant cases.[5] Further improvements in potency and different adverse—reaction profiles have been achieved with the even newer bosutinib, ponatinib, and radotinib,[6,7] but these are regarded as second-line treatments after prior TKI therapy failure.[8] When available, molecular testing for major molecular response (MMR) every 3 months is the monitoring method recommended for determining treatment efficacy.[9]

Therapeutic drug monitoring (TDM) consists of the measurement of drug concentration in biological fluids to assist in drug prescribing.[10] It can help to predict the clinical outcome of a dose regimen when the obtained concentration is compared to the therapeutic range. TDM is recommended when: (1) a drug exhibits significant pharmacokinetic variability; (2) the relationship between plasma concentration and clinical end points is predictable (ie, a therapeutic range has been defined); and (3) the therapeutic range is narrow.[11,12] TKIs used in CML treatment are subject to pharmacokinetic variability.[13] Steady-state plasma imatinib concentrations can vary within 2 orders of magnitude after the same oral dose.[14] Nilotinib is metabolized differently, depending on the uridine diphosphate glucuronosyltransferase (UGT) 1A1 genotype, which is highly dependent on a patient's ethnic origin.[13,15] Plasma dasatinib concentration is lowered in patients with the *BCR-ABL* T315I mutation, which can be acquired during treatment.[13,16]

In 2007, a research group in Bordeaux found a significant difference in steady-state trough plasma imatinib levels (C_{min}) between patients achieving and not achieving MMR, setting the efficacy threshold at 1002 ng/mL.[17] Similarly, nilotinib and dasatinib were studied to determine the relationship between C_{min} and efficacy and tolerability parameters.[18,19] Several studies were carried out in this respect and led to a wide range of results, some contrary to the initial premise.[20]

The aims of the present study were to update and discuss the relationship between TKI C_{min} and efficacy and tolerability end points, and to establish a therapeutic range for each drug if possible. Imatinib, nilotinib, and dasatinib were chosen as the TKIs to be examined in this study, given their role as first-line agents, the relatively wider clinical experience, and the availability of studies regarding TDM with them when compared to bosutinib, ponatinib, and radotinib. The working hypothesis was that a lower C_{min} would correlate with a lower MMR rate, and that a higher C_{min} would correlate with a higher frequency and severity of adverse reactions, with the use of these 3 TKIs.

Our objectives were: (1) to calculate the difference in mean C_{min} between patients achieving a response equal to or greater than MMR and patients not achieving this level of response; (2) to calculate the difference in mean C_{min} between patients presenting with adverse events and those not; and (3) to determine 2 values of drug concentration that predict MMR and the presence of adverse reactions with the maximum sensitivity and specificity in order to establish a therapeutic range. Finally, a conclusion regarding the utility of TDM of each TKI in CML was expected to be derived from the findings from this study.

MATERIALS AND METHODS

A systematic review of the available literature until February 2018 was performed. The protocol and its necessary modifications were approved by our local clinical research ethics committee. The protocol was registered in Prospero (accessible at: https://www.crd.york.ac.uk/PROSPEROFILES/92776_PROTOCOL_20180402.pdf).

A search was conducted in Medline, Cochrane Central Register of Controlled Trials (Central), EU Clinical Trials Register, and ClinicalTrials.gov for randomized clinical trials, nonrandomized controlled studies, interrupted time series studies, and case series studies that provided information about plasma levels of imatinib, nilotinib, or dasatinib and about relevant clinical end points in adult patients with chronic-phase CML treated with the corresponding TKI as the single antiproliferative therapy. The references of included studies were screened to amplify the search (the full search strategy can be found in Section Appendix A).

All titles and abstracts were screened for eligibility, and they were included or not in the review, with a reason for their exclusion. Articles were excluded if: (1) the clinical outcomes (eg, MMR rate or adverse events) were not specified; (2) participants in the study were not adult patients with chronic-phase CML; (3) they did not report data about TKI C_{min}; (4) they were reviews or nonclinical experimental studies; (5) they did not relate to CML and TKI therapy; and/or (6) they were duplicates.

Data relating C_{min} to clinical outcomes were extracted from each included study. The 2013 European LeukemiaNet recommendations[9] were followed to define *MMR* and *chronic phase*. If MMR assessment was performed more than once in a study, data regarding the time closest to 12 months after diagnosis were included in the analysis. If MMR was not reported as an efficacy outcome, the efficacy data were excluded from the analysis. Any information regarding adverse reactions was considered relevant. Risk for bias in included studies was assessed with the Cochrane Risk for Bias Tool (Cochrane Collaboration).[21]

Two dichotomous variables were the main dependent variables: the occurrence of adverse reactions (occurrence vs no occurrence) and the achievement of MMR (achievement vs no achievement). We chose MMR rate as the efficacy outcome variable because it substitutes complete cytogenetic response, which was used in previous studies, as the standard method of evaluating treatment response.[9]

Extracted data on each TKI were statistically analyzed using SPSS software version 21.0 (IBM Corp, Armonk, NY) to plot receiver operating characteristic (ROC) curves that assessed the validity (represented by the AUC) of C_{min} as a predictor of MMR achievement and of the occurrence of adverse reactions, as well as to obtain cutoff concentration values with maximum sensitivity and specificity for each of these events. The difference in mean C_{min} between groups of patients with opposite clinical outcomes was determined via a meta-analysis if possible (ie, if central tendency, dispersion, and group size measurements were provided). Review Manager software version 5.3 (Cochrane Collaboration) was used for performing the meta-analyses. When dispersion measurements were lacking, C_{min} values between groups of patients with opposite clinical outcomes were compared considering only central tendency measurements and the square root of the group size, with an independent-samples Student *t* test (SPSS version 21.0). A third analysis was performed to plot the percentage of patients who achieved MMR or experienced adverse events depending on their C_{min} TKI range.

Individual patients' data were given priority over aggregate data if the former were available. If the study results were expressed as median and range or interquartile range, the mean (SD) values were estimated in accordance with the *BMC Medical Research Methodology* journal.[22,23]

RESULTS

Study Inclusion and Exclusion

A total of 324 studies (222 for imatinib, 56 for nilotinib, and 46 for dasatinib) were identified in the search. After the application of the exclusion criteria, 38 studies were included: 28 for imatinib,[14,17,20,24–49] 7 for nilotinib,[50–56] and 3 for dasatinib.[19,57,58] The main reasons for exclusion were the study design, which included 3 narrative reviews, a lack of reporting of plasma drug levels, and the finding of duplicate studies (28%, 21%, and 14% respectively). Flow diagrams of the search results and complete references of the included studies appear in Figure 1 (the main reasons for exclusion for each TKI can be found in Section Appendix A).

Across all included studies, performance and detection bias, both due to lack of blinding, were the factors most frequently detected as having a high risk (34 studies, 89%), followed by selection bias due to a lack of allocation concealment (28 studies, 74%) (a table of risk for bias identified in each study can be found in Section Appendix A).

Imatinib

The results from the 19 studies that provided at least measures of central tendency and dispersion for imatinib C_{min} and MMR achievement were combined in a meta-analysis (Figure 2), which accounted for a total of 4563 patients. Briefly, 2630 (58%) had achieved MMR and 1933 (42%) had not. As the studies were heterogeneous ($I^2 = 80\%$), the random-effects method was chosen. The mean (SD) C_{min} values were 1193.8 ng/mL (525.3) in the group with MMR and 989.6 ng/mL (483.1) in the group without MMR. The difference in mean C_{min} was 204.2 ng/

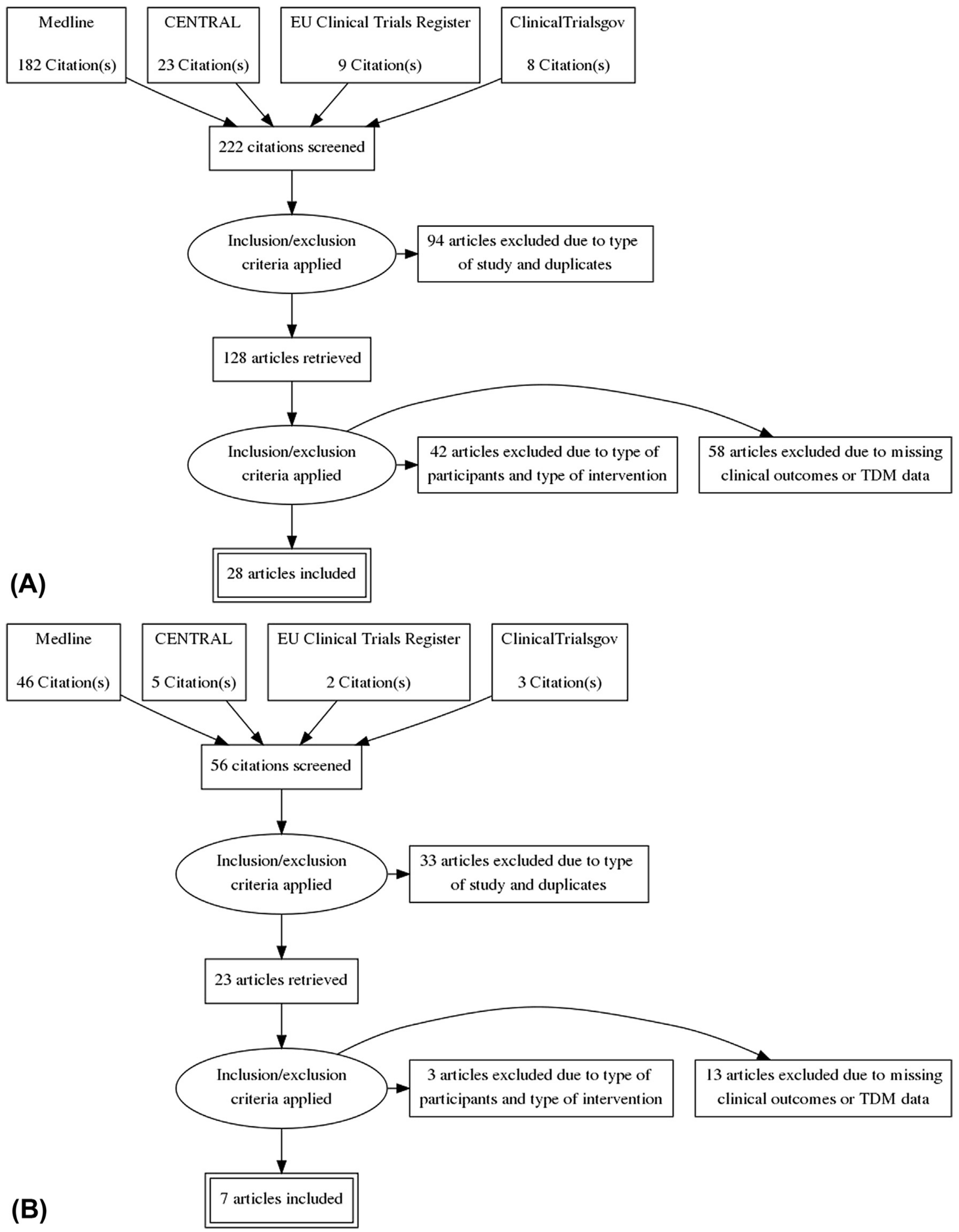

Figure 1. Flow diagrams of articles regarding review of imatinib (A), nilotinib (B), and dasatinib (C). TDM = therapeutic drug monitoring.

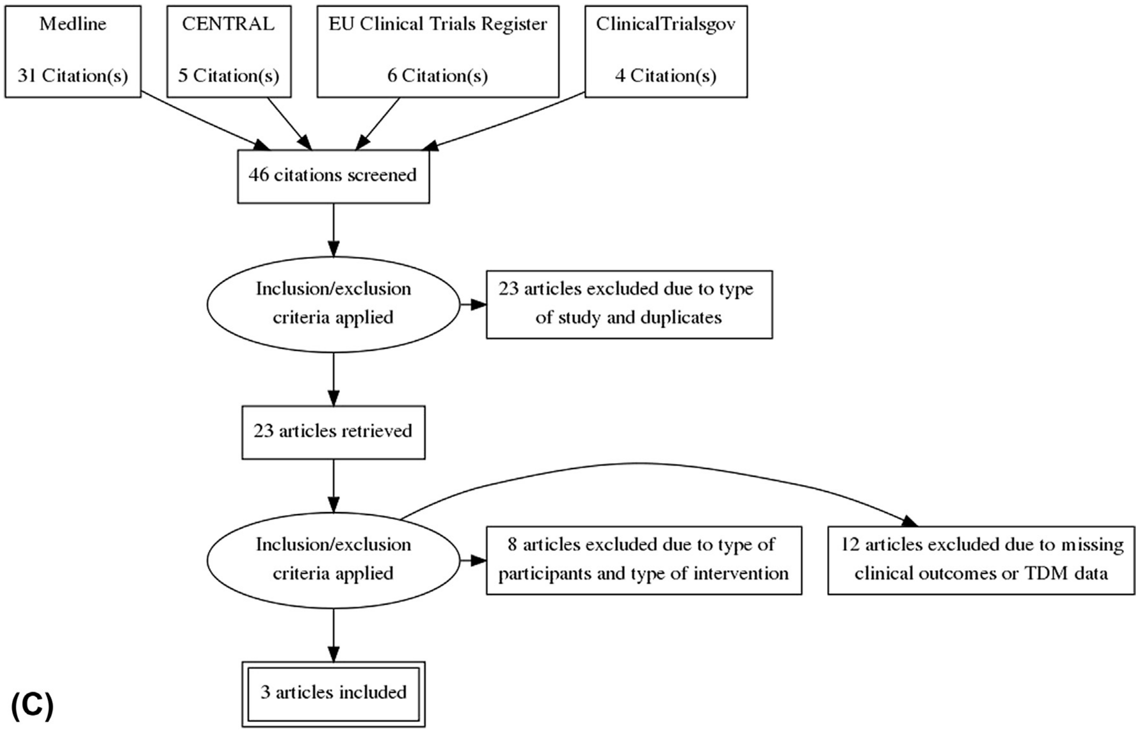

Figure 1. (*continued*).

mL, with a 95% CI of 124.7–283.8. A funnel plot (Figure 3) indicates a low risk for reporting bias.

Data from 2 studies that did not report a measure of statistical dispersion[26,30] were added to those previously used in the meta-analysis (n = 4623) to plot a ROC curve (Figure 4), which had an AUC of 0.673 (95% CI, 0.614–0.732). The optimal cutoff value of C_{min} was 1000.1 ng/mL, with a sensitivity of 0.60 and a specificity of 0.66 for predicting MMR.

The results from 4 studies that reported C_{min} and information about adverse events were combined in a meta-analysis (Figure 5). In them, 268 patients (27%) were reported to have presented with at least 1 adverse event of any kind, and 723 (73%) were not. Mean (SD) C_{min} values were 1286.2 (638.7) ng/mL in the group with adverse events and 1183.9 (645.6) ng/mL in the group without adverse events, with a statistically nonsignificant difference in means of 102.4 ng/mL (95% CI, –59.0 to 263.9) using the random-effects method (I^2 = 48%). A ROC curve was plotted that included data from these 4 studies plus 1 study that did not report enough information to have been included in the meta-analysis[30] (n = 1051). The AUC was 0.587 (95% CI, 0.477–0.696), with a cutoff C_{min} value of 1397.4 ng/mL (sensitivity, 0.56; specificity, 0.83) to predict adverse events (for all ROC curves, see Section Appendix A).

The percentages of patients achieving MMR and presenting with adverse events depending on the range of imatinib C_{min} are represented in Figure 6A, and suggest a therapeutic range of imatinib C_{min} of 1000–1500 ng/mL because a value of >1500 ng/mL would have increased the probability of toxicity without increasing the probability of efficacy.

Nilotinib

The results from the studies referring to the relationship between nilotinib C_{min} and the achievement of MMR could not be combined in a meta-analysis because the studies did not report statistical dispersion measurements. Four studies provided information about 654 patients. The results were combined only to consider the measure of central tendency and the square root of the group size. The mean (SD) C_{min} in the group that had achieved MMR (n = 315) was 1075.2 (374.0)

Study or Subgroup	MMR Mean	MMR SD	MMR Total	No MMR Mean	No MMR SD	No MMR Total	Weight	Mean Difference IV, Random, 95% CI	Year
Picard, 2007	1,452	649	34	869	427	34	5.1%	583.00 [321.87, 844.13]	2007
Larson, 2008	1,006	328	184	950	315	167	10.3%	56.00 [-11.29, 123.29]	2008
Kawaguchi, 2009	1,640	710	16	1,470	490	11	2.4%	170.00 [-282.64, 622.64]	2009
Forrest, 2009	1,067	473	51	1,063	643	27	4.8%	4.00 [-271.09, 279.09]	2009
Takahashi, 2010-B	1,107	594	166	873	529	88	8.2%	234.00 [91.24, 376.76]	2010
Ishikawa, 2010	1,224	371	38	818	221	22	8.0%	406.00 [256.19, 555.81]	2010
Awidi, 2010	2,767	781	49	1,763	629	54	4.8%	1004.00 [728.38, 1279.62]	2010
Takahashi, 2010-A	888	383	34	650	306	28	7.3%	238.00 [66.48, 409.52]	2010
Faber, 2010	1,720	1,537	192	2,235	2,659	77	1.4%	-515.00 [-1147.45, 117.45]	2010
Yoshida, 2011	1,044	636	27	818	488	11	3.2%	226.00 [-149.12, 601.12]	2011
Koren-Michowitz, 2012	976	385	120	862	347	27	8.0%	114.00 [-33.91, 261.91]	2012
White, 2012	2,036	1,069	100	1,642	860	38	3.6%	394.00 [49.52, 738.48]	2012
NCT00124748	953	1,657	205	994	1,713	271	4.2%	-41.00 [-346.03, 264.03]	2012
Ohnishi, 2012	1,140	436	47	1,148	439	3	2.0%	-8.00 [-520.17, 504.17]	2012
Seong, 2013	1,380	749	13	1,341	680	69	2.5%	39.00 [-398.63, 476.63]	2013
Gotta, 2014-A	1,459	838	6	1,342	794	14	0.9%	117.00 [-672.05, 906.05]	2014
Gotta, 2014-B	870	326	1286	790	304	944	11.0%	80.00 [53.66, 106.34]	2014
Rousselot, 2015	935	129	43	854	127	43	10.6%	81.00 [26.89, 135.11]	2015
Ostojic, 2016	1,574	598	19	1,163	585	5	1.6%	411.00 [-167.99, 989.99]	2016
Total (95% CI)			**2630**			**1933**	**100.0%**	**204.23 [124.65, 283.81]**	

Heterogeneity: Tau² = 14806.79; Chi² = 90.33, df = 18 (P < 0.00001); I² = 80%
Test for overall effect: Z = 5.03 (P < 0.00001)

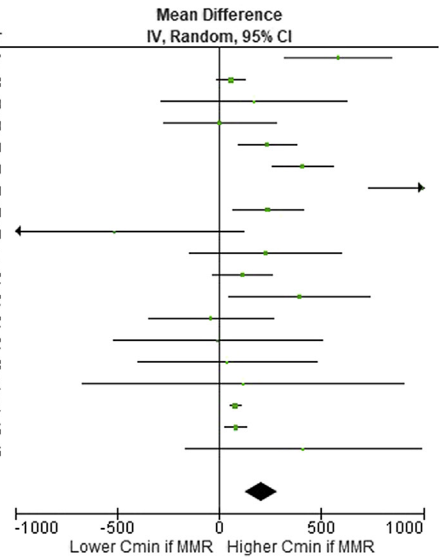

Figure 2. Difference of means meta-analysis and forest plot of studies regarding imatinib efficacy.

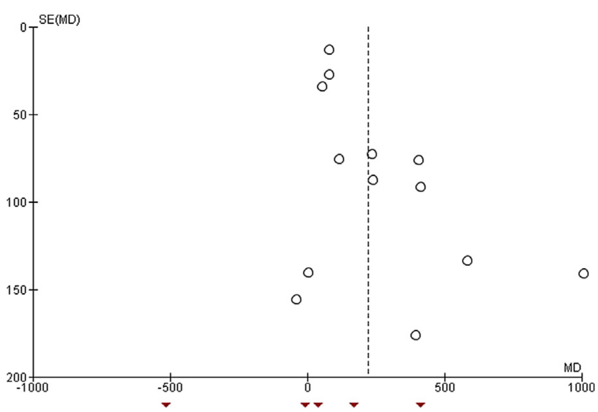

Figure 3. Funnel plot of studies about the relationship between C_{min} and imatinib efficacy. Mean C_{min} difference in ng/mL is represented in the x axis. The y axis displays SE in a reversed scale. The white dots represent studies. The arrowheads represent studies out of the graph's scale. The dotted line is set in $x = 204.2$ ng/mL (ie, the combined estimated difference).

ng/mL. The mean (SD) C_{min} in the group that had not achieved MMR ($n = 339$) was 1025.7 (408.4) ng/mL. The difference in means was not statistically significant ($p = 0.536$). The ROC curve had an AUC of 0.534 (95% CI, 0.419–0.649), with no optimal cutoff value found (ie, no C_{min} value had both sensitivity and specificity above 0.5) (see Section Appendix A).

Results about C_{min} and adverse events due to nilotinib were available from 538 patients. As in the previous comparison, dispersion measurements were not provided; hence, only central tendency measurements and group size could be used to compare the 2 groups, rendering a meta-analysis unfeasible. A total of 29 patients (5%) were reported to have had at least 1 adverse event, with a mean (SD) C_{min} of 1291.4 (353.6) ng/mL. A total of 509 patients (95%) were not reported to have had any adverse events, with a mean (SD) C_{min} of 1185.9 (368.7) ng/mL. The difference in means was not statistically significant ($p = 0.414$). The ROC curve had an AUC of 0.568 (95% CI, 0.377–0.759). No C_{min} value had both sensitivity and specificity above 0.5 for adverse events (see Section Appendix A).

The percentages of patients achieving MMR and presenting with adverse events depending on the range of nilotinib C_{min} are represented in Figure 6B, which shows that no therapeutic range could be defined.

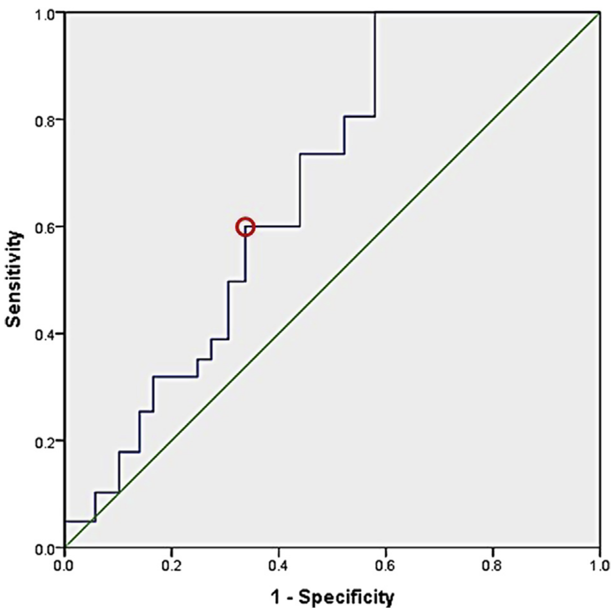

Figure 4. Imatinib efficacy receiver operating characteristic curve. Sensitivity and false-positive rate of predicting major molecular response with imatinib C_{min}. The circle marks the point corresponding to $C_{min=}$1000.1 ng/mL.

Dasatinib

Two studies[57,58] reported results about C_{min} and MMR achievement, but did not provide necessary dispersion measurements to allow for a meta-analysis. Results from 340 patients were combined. The group that achieved MMR (n = 281) had a mean (SD) C_{min} of 1.22 (0.398) ng/mL. The group that did not achieve MMR (n = 59) had a mean (SD) C_{min} of 1.23 (0.422) ng/mL. The ROC curve had an AUC of 0.491 (95% CI, 0.304–0.677), with no identifiable C_{min} value optimal for predicting MMR (see Section Appendix A).

Two of the studies of dasatinib[19,57] reported results on C_{min} and adverse events, but they did not report the statistical dispersion measurements. Central tendency measurements and group size data from 856 patients were analyzed. The group of patients reported to have had at least 1 adverse event (n = 141) had a mean (SD) C_{min} of 3.42 (2.03) ng/mL. The group reported not to have had any adverse events (n = 715) had a mean (SD) C_{min} of 3.26 (2.01) ng/mL. The difference in means was not statistically significant (p = 0.720). The ROC curve evaluating the utility of dasatinib C_{min} in predicting adverse events had an AUC of 0.523 (95% CI, 0.399–0.646). The optimal C_{min} cutoff value was identified as 3.165 ng/mL (sensitivity, 0.50; specificity, 0.53) (see Section Appendix A).

The percentages of patients achieving MMR and presenting with any adverse event, depending on the range of dasatinib C_{min}, are represented in Figure 6C, which shows that no therapeutic range could be defined.

DISCUSSION

Most of the studies included in this systematic review were observational (n = 24), with few (n = 14) clinical trials reported.[19,30,31,35–38,40,48,52,53,55–57] Among the clinical trials, several were open-label studies. These findings explain the high risk for selection, performance, and detection biases due to the lack of randomization and lack of blinding. Regarding attrition bias, while hematopoietic stem cell transplantation is no longer preferable in Chronic-phase CML since the adoption of TKIs, there could still be circumstances in which hematopoietic stem cell transplantation HSCT may

	Presenting Adverse Events			No Adverse Events				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Larson, 2008	1,091.4	395.1	15	974.2	318	336	29.2%	117.20 [-85.62, 320.02]	2008
NCT00124748	924.8	1,615.9	163	1,006.2	1,729.7	310	17.8%	-81.40 [-395.43, 232.63]	2012
Gotta, 2014	1,324.7	699.2	28	1,423	734.5	28	13.8%	-98.30 [-473.92, 277.32]	2014
Francis, 2015	1,581.7	355.1	62	1,336.5	366.1	49	39.2%	245.20 [109.85, 380.55]	2015
Total (95% CI)			**268**			**723**	**100.0%**	**102.44 [-59.04, 263.92]**	

Heterogeneity: Tau² = 12528.88; Chi² = 5.76, df = 3 (P = 0.12); I² = 48%
Test for overall effect: Z = 1.24 (P = 0.21)

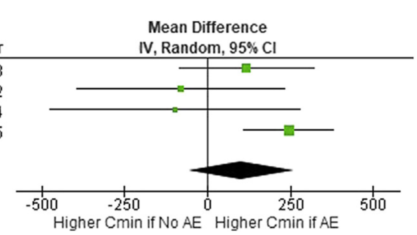

Figure 5. Differences in means in meta-analysis and forest plot of studies regarding imatinib tolerability.

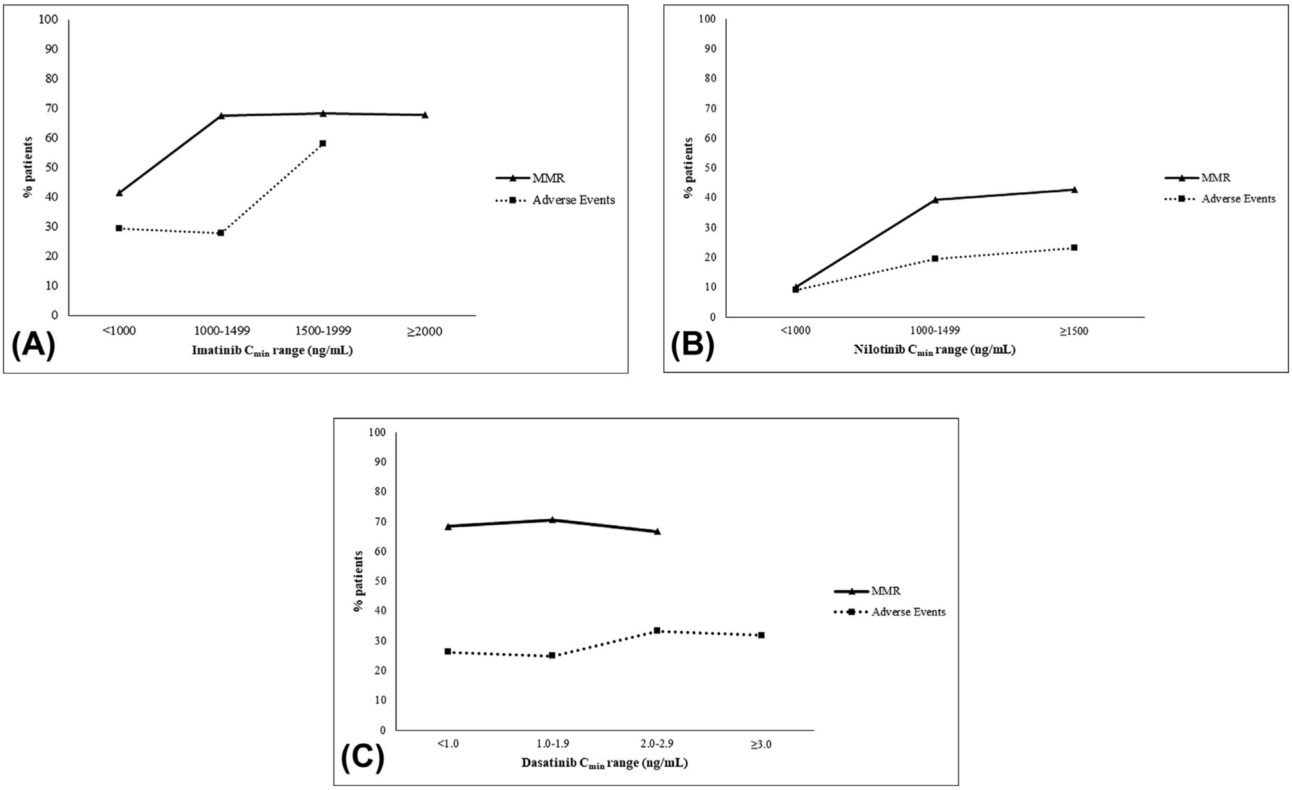

Figure 6. Percentages of patients presenting with major molecular response (MMR) or adverse events, depending on the C_{min} ranges of imatinib (A), nilotinib (B), and dasatinib (C).

be used, such as in young patients with human leukocyte antigen–matched related sibling donors. Thus, the MMR rates should account for differential attrition rates between patients who reached and did not reach MMR, but we did not have this information to be analyzed in our study.

Imatinib

The findings from the present systematic review support that TDM is useful in identifying a cause of insufficient response to imatinib in nonresponders, and in facilitating a recommendation of increasing the imatinib dosage if C_{min} is low.

The ROC analysis in the systematic review indicated that 1000 ng/mL was the imatinib C_{min} value that best predicted the achievement of MMR, with moderate sensitivity (0.60) and specificity (0.63) values. The overall validity of the ROC curve was also moderate, with an AUC between 0.614 and 0.732. Given these reasons, we recommend the 1000 ng/mL threshold established by Picard et al[17] and endorsed by a further review.[13] Based on our results, we recommend early imatinib TDM, before molecular response assessment (ie, 3 months after treatment onset), for help in predicting clinical efficacy. The rather limited sensitivity and specificity values imply that TDM is not infallible in predicting imatinib efficacy. Our recommendation is to use it as a tool in combination with other useful information sources, such as clinical history, physical examination, and other specific laboratory parameters, which could increase the predictive value of TDM.

The present systematic review did not offer a significant difference in imatinib C_{min} between patients with and without adverse events. A comparison of C_{min} between patients with adverse events of different severities was unfeasible, given the heterogeneity in the reporting of these outcomes, for any TKI. We were unable to find significant differences in values between groups of patients with and without adverse events in the meta-analysis of imatinib tolerability, probably due to the lack of individual patients' data, the variability of adverse events reported, and the low number of TDM studies found to have reported on these outcomes.

In the attempt to find an upper limit of the therapeutic range of imatinib, one concentration value was pointed out, ~1400 ng/mL, derived from the ROC analysis and from the percentage of patients presenting with adverse events and with a C_{min} of >1500 ng/mL (Figure 6A). Nonetheless, it was backed with evidence insufficient for strongly recommending it as a threshold for giving clinical management recommendations, but it suggests that the upper limit of the range of imatinib considered as therapeutic should be lower than the current 3000 ng/mL.[12] Guilhot et al[59] found an association between higher rates of hematologic adverse events and an imatinib C_{min} of >3180 ng/mL. If we compare it with the value for the tolerability limit that surfaced in our study, 3000 ng/mL would be highly specific, but probably lacking in sensitivity. Therefore, we suggest a therapeutic range of 1000−1500 ng/mL, yet further studies are advisable to reach a consensus about an imatinib C_{min} tolerability threshold. A prospective study that systematically enrolls patients in a routine clinical environment would provide better-quality evidence than would a retrospective case series description. Further studies that evaluate the relationship between peak plasma imatinib concentration and the appearance of adverse events would also be of interest.

In our analysis, we did not include other covariates, such as age, sex, dose, time since diagnosis, previous treatment, or genetic polymorphisms, which may influence the response to treatment. This limitation may inhibit the understanding of the potential impact of the proposed new concentration range of imatinib.

The relationship between different imatinib doses and their efficacy and tolerability outcomes, while relevant to the clinical management of patients with chronic-phase CML,[60] lies outside of the scope of this review. Our study focused on the achieved drug plasma concentration, which varies depending on the dose and the pharmacokinetic parameters in each case. This applies to the 3 TKIs included here. More detailed studies regarding the benefits of TDM in specific situations, such as a high-dose therapy, could better establish the role of TDM in these patients.

Nilotinib

The results from the systematic review showed a tendency toward higher C_{min} in patients who achieved MMR or experienced adverse events when compared respectively to patients without MMR or who did not experience adverse events. This tendency is consistent with the working hypothesis that TDM would detect groups of patients with opposite clinical outcomes based on their nilotinib C_{min}. However, neither of the mentioned differences was statistically significant, and no therapeutic range limits could be spotted in the ROC analysis. This is in keeping with the findings of Larson et al,[52] in which no significant difference in C_{min} values was found between patients achieving and not achieving response. On the other hand, Giles et al[51] found a significant difference in the time to response depending on nilotinib $C_{min.}$ In their study, a group with a C_{min} of <553 ng/mL presented a significantly longer time to MMR than a group with a C_{min} of >553 ng/mL.[51] The median nilotinib C_{min} in their study was 766 ng/mL,[51] lower than the ranges of central tendency measurements in our study, around 1000 ng/mL.

Our lack of precision in detecting significant differences might have been due to the main limitations that the systematic review was subject to: (1) the use of aggregated data instead of individual patients' data decreased the likelihood of finding a real difference between groups; (2) the conversion of medians and ranges into estimated means (SD) improved the comparability of study results at the cost of a higher risk for misrepresenting central tendency measurements; (3) adverse events were not homogeneously reported, preventing the inclusion of only severe adverse events in the analysis; (4) included studies had heterogeneous designs and objectives and many of them were not specifically designed to detect differences between the groups of interest to the present study; and (5) the conversion of dependent variables in dichotomic variables.

It was surprising to find such a low efficacy rate for nilotinib (Figure 6B) when compared to the other TKIs (Figure 6A, C) in the systematic review. This finding could have been partly explained because 2 studies (Giles[51] and Takahashi[55]; combined $n = 112$) included only imatinib-resistant or imatinib-intolerant patients, who would presumably have shown less response to nilotinib too. However, the study with the most participants[52] included 405 newly diagnosed patients, and it also presented an overall MMR rate at 12 months of around 50%. These efficacy results seem less unexpected when compared to those achieved in other studies,[61] with MMR rates of <50% at 12 months.

In the present study, we were unable to predict clinical outcomes with TDM in patients with chronic-phase CML undergoing nilotinib therapy. This finding suggests that, if differences in concentration exist among patients with opposite outcomes, they would be so small that a therapeutic range for nilotinib might not be operational in clinical practice. Other authors[13] recommended measuring nilotinib C_{min} periodically from the beginning of the treatment, with a different target C_{min} depending on the UGT1A1 genotype, in a range between 500 and 800 ng/mL. The latter recommendation was based on the findings from studies that showed a relationship between C_{min} and clinical outcomes,[18,50,51,56] which we could not reproduce in our study.

Dasatinib

The systematic review search included only 3 suitable studies about dasatinib, and only one[57] provided information on both efficacy and tolerability. The efficacy results were surprising, with the finding of almost the same mean C_{min} among patients with (1.22 ng/mL) and without (1.23 ng/mL) MMR. This finding is partially explained because dasatinib efficacy seems to be more related to pharmacokinetic parameters involving C_{max} (above 50 ng/mL)[13] and the time above a certain concentration value (>12.8 hours above 4.3 ng/mL)[58] than to C_{min}. In this study we focused on C_{min} for all 3 TKIs, and we found it useful for reproducing the same results as in the cited studies[57,58] regarding C_{min}. Further research to directly evaluate other pharmacokinetic parameters is advisable to give a complete recommendation regarding dasatinib TDM.

The mean C_{min} values were very similar between groups with opposite tolerability outcomes in the systematic review. The suggested cutoff value in the ROC analysis, ~3.2 ng/mL, despite the low validity of the curve (AUC was centered at 0.5), was close to the 2.5 ng/mL recommended by Miura et al.[13] Nonetheless, the results question the 2.5 ng/mL C_{min} tolerability limit for dasatinib, since the group of patients without adverse reactions had a mean C_{min} above this limit regardless of the C_{min} measurement. To provide further information about this matter, we recommend a prospective study in which patients are systematically enrolled from routine clinical settings from the beginning of treatment with dasatinib.

CONCLUSIONS

In this study we calculated the difference in mean C_{min} between patients achieving and not achieving MMR, and between patients presenting and not presenting with adverse reactions. The difference was statistically significant regarding only imatinib efficacy. The patients treated with dasatinib presented a similar C_{min} regardless of their efficacy outcomes. The rest of the comparisons showed a tendency toward a higher C_{min} in patients with response or with adverse events, but these findings could not be confirmed. A recommended C_{min} range for imatinib (1000−1500 ng/mL) could be determined, but therapeutic ranges for the rest of the TKIs could not be determined. We conclude that TDM was found useful in predicting efficacy outcomes in adult patients with chronic-phase CML treated with imatinib. Further research is needed before TDM of nilotinib and dasatinib use in the treatment of CML can be recommended in routine clinical practice.

FUNDING

No one else other than the authors helped write or revise the manuscript.

ACKNOWLEDGMENTS

Research by D. Koller is cofinanced by H2020 Marie Sklodowska-Curie Innovative Training Network grant 721236. Research by P. Zubiaur is cofinanced by Consejería de Educación, Juventud y Deporte from Comunidad de Madrid and by European Social Fund Grant PEJD-2017-PRE/BMD-|4164|.

M. García-Ferrer contributed to study design, preparation of protocol, literature collection, selection and inclusion of data extraction and analysis, results interpretation, manuscript writing, figure generation, and manuscript revising. F. Abad-Santos contributed to study design, preparation of protocol, review of literature search, results interpretation, manuscript writing, figure generation, and manuscript revising. A. Wojnicz, G. Mejía, D. Koller and P. Zubiaur

contributed to results interpretation and manuscript revising.

DISCLOSURES

F. Abad Santos has received consultant's or investigator's fees from Abbott, Alter, Chemo, Cinfa, FAES, Farmalíder, Ferrer, GlaxoSmithKline, Galenicum, Gilead, Janssen-Cilag, Kern, Normon, Novartis, Servier, Silverpharma, Teva, and Zambon. There was been no involvement of funding sources in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The authors have indicated that they have no conflicts of interest with regard to the content of this article.

REFERENCES

1. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999;340:1330–1340.
2. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med*. 2001;344: 1038–1042.
3. Kantarjian HM, Sawyers CL, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med*. 2002;346:645–652.
4. Kantarjian HM, Cortes JE, O'Brien S, et al. Imatinib mesylate therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: high incidence of early complete and major cytogenetic responses. *Blood*. 2003;101:97–100.
5. Sawyers CL. Even better kinase inhibitors for chronic myeloid leukemia. *N Engl J Med*. 2010;363:2314–2315.
6. Pophali PA, Patnaik MM. The role of new tyrosine kinase inhibitors in chronic myeloid leukemia. *Cancer J*. 2016;22: 40–50.
7. Eskazan AE, Keskin D. Radotinib and its clinical potential in chronic-phase chronic myeloid leukemia patients: an update. *Ther Adv Hematol*. 2017;8:237–243.
8. Ruiz-Cordell K, Haimowitz S, Gracie-King L, Middleton D. Optimizing the use of TKIs in the management of chronic myelogenous leukemia. *Clin Lymphoma Myeloma Leuk*. 2016;16:442–446.
9. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122:872–884.
10. Kang JS, Lee MH. Overview of therapeutic drug monitoring. *Korean J Intern Med*. 2009;24:1–10.
11. Lewis R, Brüggemann R, Padoin C, et al. *Triazole antifungal therapeutic drug monitoring*. In: *Proceedings and Abstracts of the 6th Annual Meeting of the ECIL*. vol.12. 2015. September.
12. Ghiculescu RA. Therapeutic drug monitoring: which drugs, why, when and how to do it. *Aust Prescr*. 2008;31:42–44.
13. Miura M. Therapeutic drug monitoring of imatinib, nilotinib and dasatinib for patients with chronic myeloid leukemia. *Biol Pharm Bull*. 2015;38:645–654.
14. Li QB, Chen C, Chen ZC, et al. Imatinib plasma trough concentration and its correlation with characteristics and response in Chinese CML patients. *Acta Pharmacol Sinica*. 2010;31:999–1004.
15. Takano M, Sugiyama T. UGT1A1 polymorphisms in cancer: impact on irinotecan treatment. *Pharmgenomics Pers Med*. 2017;10:61–68.
16. Takahashi N, Miura M, Scott SA, Niioka T, Sawada K. Pharmacokinetics of dasatinib for Philadelphia-positive acute lymphocytic leukemia with acquired T315I mutation. *J Hematol Oncol*. 2012;5:23.
17. Picard S, Titier K, Etienne G, et al. Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia. *Blood*. 2007;109:3496–3499.
18. Larson RA, Yin OQP, Hochhaus A, et al. Population pharmacokinetic and exposure-response analysis of nilotinib in patients with newly diagnosed Ph+ chronic myeloid leukemia in chronic phase. *Eur J Clin Pharmacol*. 2012;68:723–733.
19. Wang X, Roy A, Hochhaus A, Kantarjian HM, Chen TT, Shah NP. Differential effects of dosing regimen on the safety and efficacy of dasatinib: retrospective exposure–response analysis of a Phase III study. *Clin Pharmacol*. 2013;5:85–97.
20. Faber E, Friedecký D, Mičová K, et al. Imatinib trough plasma levels do not correlate with the response to therapy in patients with chronic myeloid leukemia in routine clinical setting. *Ann Hematol*. 2010;91:923–929.
21. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. *BMJ*. 2001;343:d5928.
22. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
23. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
24. Wojnicz A, Colom-Fernández B, Steegman JL, Muñoz-Calleja C, Abad-Santos F, Ruiz-Nuño A. Simultaneous determination of imatinib, dasatinib, and nilotinib by liquid chromatography-tandem mass spectrometry and its application to therapeutic drug monitoring. *Ther Drug Monit*. 2017;39:252–262.

25. Awidi A, Ayed AO, Bsoul N, et al. Relationship of serum imatinib trough level and response in CML patients: long term follow-up. *Leuk Res*. 2010;34:1573–1575.
26. Blasdel C, Egorin MJ, Lagattuta TF, Druker BJ, Deininger MW. Therapeutic drug monitoring in CML patients on imatinib. *Blood*. 2007;110:1699–1701.
27. Bouchet S, Titier K, Moore N, et al. Therapeutic drug monitoring of imatinib in chronic myeloid leukemia: experience from 1216 patients at a centralized laboratory. *Fundam Clin Pharmacol*. 2013;27:690–697.
28. Forrest DL, Trainor S, Brinkman RR, et al. Cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia are correlated with Sokal risk scores and duration of therapy but not trough imatinib plasma levels. *Leuk Res*. 2009;33:271–275.
29. Francis J, Dubashi B, Sundaram R, Pradhan SC, Chandrasekaran A. A study to explore the correlation of ABCB1, ABCG2, OCT1 genetic polymorphisms and trough level concentration with imatinib mesylate-induced thrombocytopenia in chronic myeloid leukemia patients. *Cancer Chemother Pharmacol*. 2015;76:1185–1189.
30. Golabchifar AA, Rezaee S, Ghavamzadeh A, Alimoghaddam K, Dinan NH, Rouini MR. Population pharmacokinetics of imatinib in Iranian patients with chronic-phase chronic myeloid leukemia. *Cancer Chemother Pharmacol*. 2014;74:85–93.
31. Gotta V, Widmer N, Decosterd LA, Chalandon Y, Heim D, Gregor M. Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial. *Cancer Chemother Pharmacol*. 2014;74:1307–1319.
32. Gotta V, Bouchet S, Widmer N, et al. Large-scale imatinib dose–concentration–effect study in CML patients under routine care conditions. *Leuk Res*. 2014;38:764–772.
33. Ishikawa Y, Kiyoi H, Watanabe K, et al. Trough plasma concentration of imatinib reflects BCR–ABL kinase inhibitory activity and clinical response in chronic-phase chronic myeloid leukemia: a report from the BINGO study. *Cancer Sci*. 2010;101:2186–2192.
34. Kawaguchi T, Hamada A, Hirayama C, et al. Relationship between an effective dose of imatinib, body surface area, and trough drug levels in patients with chronic myeloid leukemia. *Int J Hematol*. 2009;89:642–648.
35. Koren-Michowitz M, Volchek Y, Naparstek E, et al. Imatinib plasma trough levels in chronic myeloid leukaemia: results of a multicentre study CSTI571AIL11TGLIVEC. *Hematol Oncol*. 2012;30:200–205.
36. Larson RA, Druker BJ, Guilhot F, O'Brien SG, Riviere GJ, Krahnke T. Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study. *Blood*. 2008;111:4022–4028.
37. Novartis Pharmaceuticals. Efficacy of 400 mg versus 800 mg imatinib in chronic myeloid leukemia in chronic phase patients—tyrosine kinase inhibitor optimization and selectivity (TOPS) [ClinicalTrials.gov website. Available from: https://clinicaltrials.gov/ct2/show/results/NCT00124748?id=NCT00124748&rank=1&sect=X4301256&load=cart#othr; 2012. Accessed April 5, 2018.
38. Ohnishi K, Nakaseko C, Takeuchi J, et al. Long-term outcome following imatinib therapy for chronic myelogenous leukemia, with assessment of dosage and blood levels: the JALSG CML202 study. *Cancer Sci*. 2012;103:1071–1078.
39. Ostojic A, Sertic D, Roncevic P, et al. Comparison of branded and generic imatinib plasma concentrations in patients with chronic myelogenous leukemia: unicentric study. *Clin Lymphoma Myeloma Leuk*. 2016;16:472–476.
40. Rousselot P, Johnson-Ansah H, Huguet F, et al. Personalized daily doses of imatinib by therapeutic drug monitoring increase the rates of molecular responses in patients with chronic myeloid leukemia. Final results of the Randomized OPTIM Imatinib Study. *Blood*. 2015;126:133.
41. Seong SJ, Lim M, Sohn SK, et al. Influence of enzyme and transporter polymorphisms on trough imatinib concentration and clinical response in chronic myeloid leukemia patients. *Ann Oncol*. 2013;24:756–760.
42. Sharma SK, Kumar S, Vijayakumar AR, et al. Utility of the trough plasma imatinib level monitoring at two time points in patients with the chronic myeloid leukemia-chronic phase. *J Can Res Ther*. 2014;10:305–308.
43. Skoglund K, Richter J, Olsson-Strömberg U, et al. In Vivo cytochrome P450 3A isoenzyme activity and pharmacokinetics of imatinib in relation to therapeutic outcome in patients with chronic myeloid leukemia. *Drug Monit*. 2016;38:230–238.
44. Sohn SK, Oh SJ, Kim BS, et al. Trough plasma imatinib levels are correlated with optimal cytogenetic responses at 6 months after treatment with standard dose of imatinib in newly diagnosed chronic myeloid leukemia. *Leuk Lymphoma*. 2011;52:1024–1029.
45. Takahashi N, Miura M, Scott SA, et al. Influence of CYP3A5 and drug transporter polymorphisms on

imatinib trough concentration and clinical response among patients with chronic phase chronic myeloid leukemia. *J Hum Genet*. 2010;55:731−737.
46. Takahashi N, Wakita H, Miura M, et al. Correlation between imatinib pharmacokinetics and clinical response in Japanese patients with chronic-phase chronic myeloid leukemia. *Clin Pharmacol Ther*. 2010;88:809−813.
47. Van Obbergh F, Knoops L, Devos T, et al. The clinical relevance of imatinib plasma trough concentrations in chronic myeloid leukemia. A Belgian study. *Clin Biochem*. 2017;50:452−454.
48. White DL, Radich J, Soverini S, et al. Chronic phase chronic myeloid leukemia patients with low OCT-1 activity randomized to high-dose imatinib achieve better responses and have lower failure rates than those randomized to standard-dose imatinib. *Haematologica*. 2012;97:907−914.
49. Yoshida C, Komeno T, Hori M, et al. Adherence to the standard dose of imatinib, rather than dose adjustment based on its plasma concentration, is critical to achieve a deep molecular response in patients with chronic myeloid leukemia. *Int J Hematol*. 2011;93:618−623.
50. Abumiya M, Takahashi N, Niioka T, et al. Influence of UGT1A1 *6, *27, and *28 polymorphisms on nilotinib-induced hyperbilirubinemia in Japanese patients with chronic myeloid leukemia. *Drug Metab Pharmacokinet*. 2014;29:449−454.
51. Giles FJ, Yin OQP, Sallas WM, et al. Nilotinib population pharmacokinetics and exposure-response analysis in patients with imatinib-resistant or -intolerant chronic myeloid leukemia. *Eur J Clin Pharmacol*. 2013;69:813−823.
52. Larson RA, Yin OQ, Hochhaus A, et al. Population pharmacokinetic and exposure-response analysis of nilotinib in patients with newly diagnosed Ph+ chronic myeloid leukemia in chronic phase. *Eur J Clin Pharmacol*. 2012;68:723−733.
53. Novartis Pharmaceuticals. Tolerability and efficacy of nilotinib vs imatinib in the treatment of newly diagnosed Chinese Ph+ CML-CP patients [ClinicalTrials.gov website]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01275196?term=drug+concentration&rslt=With&cond=Chronic+Myeloid+Leukemia&intr=nilotinib&rank=1&sect=X4301256#othr; 2011. Accessed April 5, 2018.
54. Onaka T, Takahashi N, Miura M, Yonezawa A, Imada K, Sawada K. Pharmacokinetics of nilotinib in imatinib-resistant/intolerant chronic myeloid leukemia patients on hemodialysis for chronic renal failure. *Am J Hematol*. 2012;87:451.
55. Takahashi N, Miura M, Kuroki J, et al. Multicenter phase II clinical trial of nilotinib for patients with imatinib-resistant or -intolerant chronic myeloid leukemia from the East Japan CML study group evaluation of molecular response and the efficacy and safety of nilotinib. *Biomark Res*. 2014;2:6.
56. Takahashi N, Niioka T, Abumiya M, Takahashi S, Miura M. Effect of plasma trough concentration of nilotinib and polymorphisms of drug transporter genes on the frequency of adverse events in chronic phase of chronic myeloid leukemia: sTAT 1 and STAT2 trials. In: *Proceedings of the Haematologica Conference: 22th Congress of the European Hematology Association; June 22, 2017; Madrid, Spain*. 2017.
57. Bouchet S, Rousselot P, Guilhot F, et al. Dasatinib daily dose optimization based on therapeutic drug monitoring resulted in reduced risk of pleural effusions and high molecular response rates. *Fundam Clin Pharmacol*. 2015;29:9−10.
58. Ishida Y, Murai K, Yamaguchi K, et al. Pharmacokinetics and pharmacodynamics of dasatinib in the chronic phase of newly diagnosed chronic myeloid leukemia. *Eur J Clin Pharmacol*. 2016;72:185−193.
59. Guilhot F, Hughes TP, Cortes J, et al. Plasma exposure of imatinib and its correlation with clinical response in the tyrosine kinase inhibitor optimization and selectivity trial. *Haematologica*. 2012;97:731−738.
60. Gafter-Gvili A, Leader A, Gurion R, et al. High-dose imatinib for newly diagnosed chronic phase chronic myeloid leukemia patients-Systematic review and meta-analysis. *Am J Hematol*. 2011;86:657−662.
61. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251−2259.

Address correspondence to: Francisco Abad-Santos, Department of Clinical Pharmacology, Hospital Universitario de la Princesa, C/ Diego de León 62, 28006, Madrid, Spain. E-mail: francisco.abad@salud.madrid.org

APPENDIX A. SUPPLEMENTARY MATERIAL TO *UTILITY OF THERAPEUTIC DRUG MONITORING OF IMATINIB, NILOTINIB AND DASATINIB IN CHRONIC MYELOID LEUKEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS* BY MG-F, AW, GM, DK, PZ AND FA-S.

1 Full search strategies.

TKI	Database	Search strategy
Imatinib	Medline (searched through Pubmed)	("leukemia, myelogenous, chronic, bcr-abl positive"[MeSH Terms] AND ("drug monitoring"[MeSH Terms] OR "antineoplastic Agents/ pharmacokinetics*"[MeSH Terms])) AND "imatinib mesylate"[MeSH Terms]
	CENTRAL	("chronic myelogenous leukemia" or "chronic myeloid leukemia") and ("therapeutic drug monitoring" or "drug monitoring" or "plasma level" or "trough level" or "drug concentration") and "imatinib"
	EU Clinical Trials Register	chronic myeloid leukemia AND imatinib AND (drug monitoring OR drug concentration OR drug level); trials with results
	ClinicalTrials.gov	Condition: chronic myeloid leukemia Intervention: Imatinib Other terms: drug concentration/drug monitoring/drug level Studies with results
Nilotinib	Medline (searched through Pubmed)	("leukemia, myelogenous, chronic, bcr-abl positive"[MeSH Terms] AND ("drug monitoring"[MeSH Terms] OR "antineoplastic Agents/ pharmacokinetics*"[MeSH Terms])) AND "nilotinib"
	CENTRAL	("chronic myelogenous leukemia" or "chronic myeloid leukemia") and ("therapeutic drug monitoring" or "drug monitoring" or "plasma level" or "trough level" or "drug concentration") and "nilotinib"
	EU Clinical Trials Register	chronic myeloid leukemia AND nilotinib AND (drug monitoring OR drug concentration OR drug level); trials with results
	ClinicalTrials.gov	Condition: chronic myeloid leukemia Intervention: Nilotinib Other terms: drug concentration/drug

(*continued on next page*)

. (*Continued*)

TKI	Database	Search strategy
		monitoring/drug level Studies with results
Dasatinib	Medline (searched through Pubmed)	("leukemia, myelogenous, chronic, bcr-abl positive"[MeSH Terms] AND ("drug monitoring"[MeSH Terms] OR "antineoplastic Agents/ pharmacokinetics*"[MeSH Terms])) AND "dasatinib"[MeSH Terms]
	CENTRAL	("chronic myelogenous leukemia" or "chronic myeloid leukemia") and ("therapeutic drug monitoring" or "drug monitoring" or "plasma level" or "trough level" or "drug concentration") and "dasatinib"
	EU Clinical Trials Register	chronic myeloid leukemia AND dasatinib AND (drug monitoring OR drug concentration OR drug level); trials with results
	ClinicalTrials.gov	Condition: chronic myeloid leukemia Intervention: Dasatinib Other terms: drug concentration/drug monitoring/drug level Studies with results

2 Characteristics of excluded studies.

	n (% of excluded studies)			
Main reason for exclusion	**Imatinib**	**Nilotinib**	**Dasatinib**	**Total**
Study design/review	54 (28)	12 (24)	15 (35)	81 (28)
Missing TDM data	36 (19)	11 (22)	12 (28)	59 (21)
Duplicate studies	23 (12)	16 (33)	0 (0)	39 (14)
Not relating to TKI	26 (13)	3 (6)	3 (7)	32 (11)
Not a clinical study	17 (9)	5 (10)	8 (19)	30 (10)
Missing clinical outcomes	22 (11)	2 (4)	0 (0)	24 (8)
Type of participants	13 (7)	0 (0)	5 (12)	18 (6)
Type of intervention	3 (2)	0 (0)	0 (0)	3 (1)
Total excluded	**194**	**49**	**43**	**286**

3. Risk of bias.

Table 1. Risk of bias in included studies regarding imatinib.

First author, year / trial identifier	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
Blasdel, 2007	High	High	High	High	High	High	Low
Picard, 2007	High	High	Low	Low	High	High	Unclear
Larson, 2008	Low	Unclear	Low	Low	Unclear	Unclear	High
Forrest, 2009	Low	High	Low	Low	High	High	Unclear
Kawaguchi, 2009	High	High	Low	Low	High	High	Low
Awidi, 2010	High	High	Low	Low	High	High	Low
Faber, 2010	High	High	Low	Low	High	High	Unclear
Ishikawa, 2010	Unclear	High	Low	Low	High	High	Low
Li, 2010	Low	High	Low	Low	High	High	Low
Takahashi, 2010-A	High	High	Low	Low	High	High	Low
Takahashi, 2010-B	Unclear	Unclear	Low	High	High	High	Low
Sohn, 2011	Unclear	Unclear	Low	Low	High	High	Low
Yoshida, 2011	High	High	Low	Low	High	High	Low
NCT00124748	Low	High	Low	Low	High	High	Unclear
Koren-Michowitz, 2012	Unclear	High	Low	Low	Unclear	Unclear	Unclear
Ohnishi, 2012	High	High	Low	Low	High	High	Low
White, 2012	Unclear	Unclear	Low	Low	High	High	Low
Bouchet, 2013	High	High	Low	Low	Low	Low	Low
Seong, 2013	High	High	Low	Low	High	High	Low
Golabchifar, 2014	High	High	Low	Unclear	High	High	Low
Gotta, 2014-A	Low	Low	Low	Low	High	High	Low
Gotta, 2014-B	High	High	Low	Low	High	High	High
Sharma, 2014	Unclear	Low	Low	Low	Low	Low	Unclear
Francis, 2015	High	High	Low	Low	High	High	High
Rousselot, 2015	Unclear	High	Low	Low	High	High	High
Ostojic, 2016	High	High	Low	Low	High	High	Low
Skoglund, 2016	High	High	Low	Low	High	High	Low
Van Obbergh, 2017	High	High	Low	Unclear	High	High	Low

Table 2. Risk of bias in included studies regarding nilotinib.

First author, year / trial identifier	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
NCT01275196	Unclear	Unclear	Low	Low	High	High	Low
Larson, 2012	Low	Low	Low	Low	High	High	Low
Onaka, 2012	High	High	Low	High	High	High	Low
Giles, 2013	High	High	Low	Unclear	High	High	Unclear
Abumiya, 2014	Unclear	High	Low	Low	High	High	Unclear
Takahashi, 2014	Low	High	Low	Low	High	High	Low
Takahashi, 2017	High	High	Low	Low	High	High	Unclear

Table 3. Risk of bias in included studies regarding dasatinib.

First author, year / trial identifier	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
Wang, 2013	Unclear	Unclear	Low	Low	High	High	Low
Bouchet, 2015	Low	Low	Low	Low	High	High	Low
Ishida, 2016	High	High	Low	Low	High	High	Low

4. Receiver Operating Characteristic (ROC) Curves

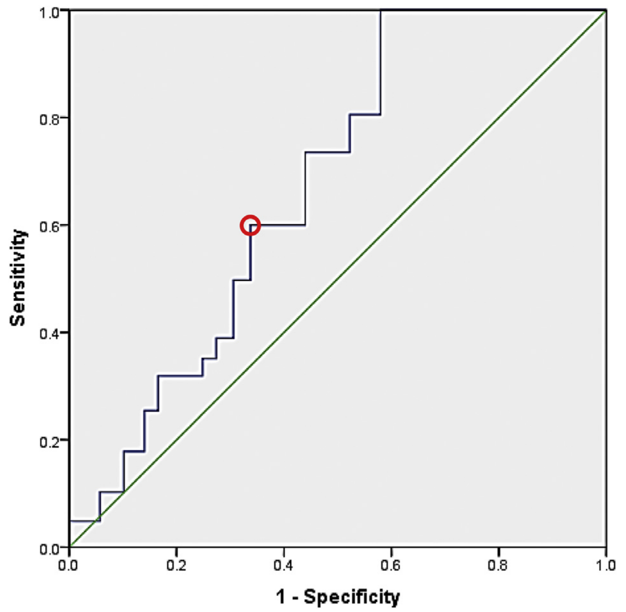

Figure 1. Imatinib efficacy ROC curve. Sensitivity and false positive rate of predicting MMR with imatinib C_{min}. The circle marks the point corresponding to C_{min}=1000.1 ng/mL.

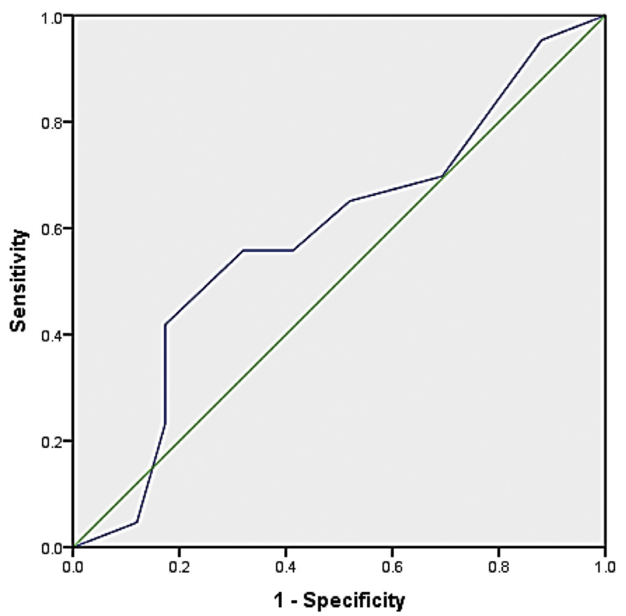

Figure 2. Imatinib safety ROC curve. Sensitivity and false positive rate of predicting adverse events with imatinib C_{min}.

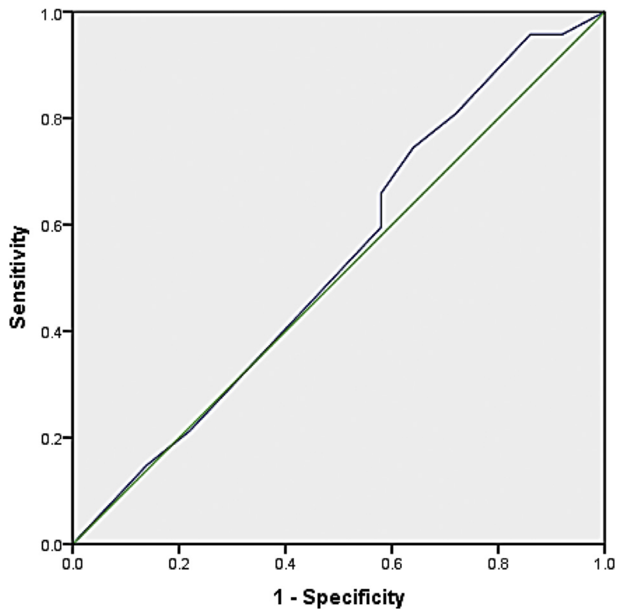

Figure 3. Nilotinib efficacy ROC curve. Sensitivity and false positive rate of predicting MMR with nilotinib C_{min}.

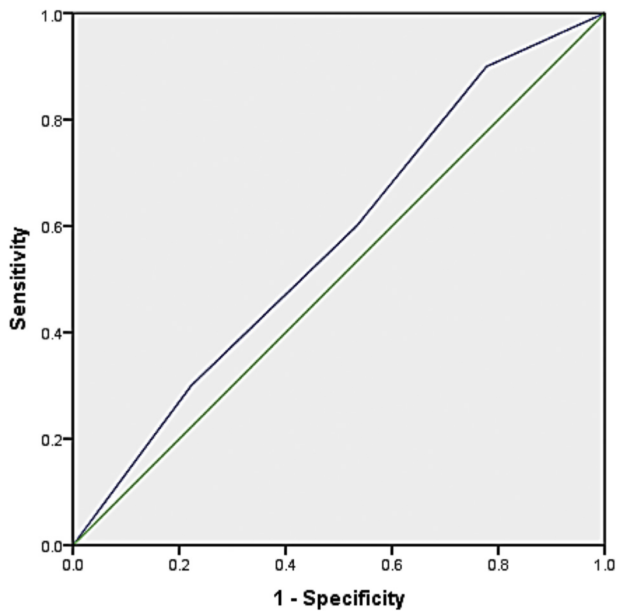

Figure 4. Nilotinib safety ROC curve. Sensitivity and false positive rate of predicting adverse events with nilotinib C_{min}.

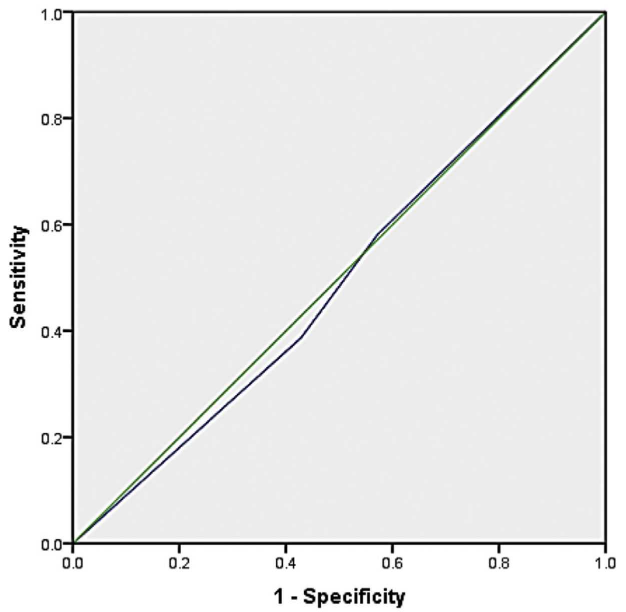

Figure 5. Dasatinib efficacy ROC curve. Sensitivity and false positive rate of predicting MMR with dasatinib C_{min}.

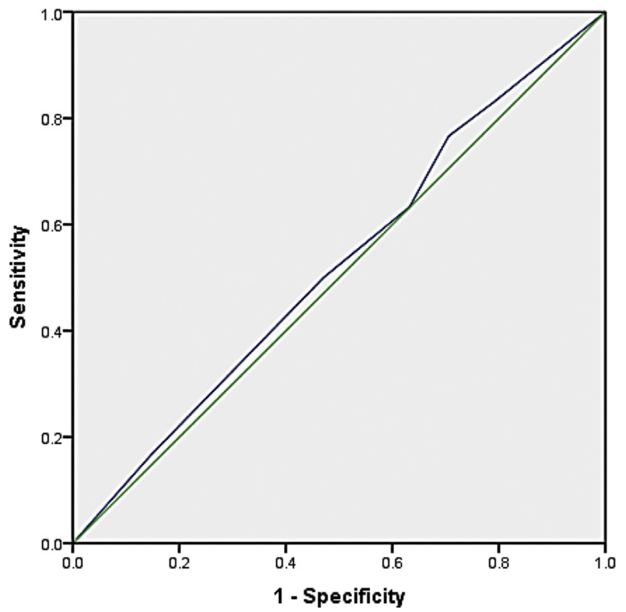

Figure 6. Dasatinib safety ROC curve. Sensitivity and false positive rate of predicting adverse events with dasatinib C_{min}.