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

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ABSTRACT

Background
The functional activity of the organic cation transporter 1 (OCT-1) protein (OCT-1 activity) is an excellent predictor of molecular response and progression-free survival in patients with newly diagnosed chronic phase chronic myeloid leukemia treated with imatinib as front-line therapy.

Design and Methods
In this study the predictive value of OCT-1 activity in patients treated with imatinib 400 mg/day or 800 mg/day was evaluated in relation to trough imatinib plasma levels assessed in 100 patients enrolled in the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) trial.

Results
The rate of major molecular responses by 24 months in patients on imatinib 400 mg/day was significantly higher in those with high OCT-1 activity than in those with low OCT-1 activity (low OCT-1 activity, 57% of patients; high OCT-1 activity, 100%; $P<0.001$); the corresponding difference in patients treated with imatinib 800 mg/day did not reach statistical significance (low OCT-1 activity, 68%; high OCT-1 activity, 95%; $P=0.073$). In addition, the combination of low trough imatinib levels (<1200 ng/mL) and low OCT-1 activity defined a group of patients who had the lowest rates of major molecular response (47%) by 24 months compared to all other patients (81%, $P=0.009$). These patients were also at the highest risk of failed imatinib therapy when compared to all other patients ($P<0.001$).

Conclusions
High-dose imatinib leads to superior molecular responses in patients with low OCT-1 activity. In this group trough imatinib levels may define a group with inferior outcomes. Among patients with high OCT-1 activity, neither higher imatinib dose nor monitoring imatinib trough levels was found to be of significant clinical value. Hence OCT-1 activity determined prior to the start of therapy in newly diagnosed CML patients provides a valuable prognostic tool to determine the optimal up-front dose of imatinib in patients with newly diagnosed chronic phase chronic myeloid leukemia.

Key words: chronic myeloid leukemia, imatinib, OCT-1 activity, imatinib trough levels.

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The online version of this article has a Supplementary Appendix.

Introduction

The organic cation transporter 1 (OCT-1) is the major active influx pump responsible for the transport of imatinib into target BCR-ABL-positive cells. Thomas *et al.*[1] demonstrated that imatinib was a substrate for OCT-1 and a number of subsequent studies linked OCT-1 mRNA expression to the outcome of patients with chronic myeloid leukemia (CML) on imatinib therapy.[2-5] We have previously demonstrated that the functional activity of the OCT-1 protein (OCT-1 activity) is predictive of both short-term and longer-term molecular responses, as well as event-free and progression-free survival[6-8] with patients who have low OCT-1 activity demonstrating significantly poorer outcomes than those with high OCT-1 activity.

Studies to date demonstrating the predictive value of OCT-1 activity have been based on the TIDEL I trial, an Australian study in which patients with newly diagnosed, chronic phase-CML (CP-CML) all received a starting dose of imatinib 600 mg/day, followed by dose escalation if they failed to achieve various pre-determined milestones.[9] The Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) trial - a randomized phase III study of imatinib 400 mg/day *versus* imatinib 800 mg/day in newly diagnosed CP-CML[10] has more recently provided the opportunity to assess the predictive value of OCT-1 activity in the setting of two dosing regimens. In addition, in this study the utility of a combination of OCT-1 activity and trough imatinib plasma levels was examined.

The TOPS trial was designed to assess the efficacy of higher imatinib dosing in the CP-CML setting. The expectation that patients treated with 800 mg/day would achieve higher rates of complete cytogenetic response and major molecular response (≤0.1% BCR-ABL on the International Scale) by the primary end-point assessment time of 12 months than those treated with 400 mg/day was not substantiated in this study.[10] While patients in the 800 mg/day cohort achieved complete cytogenetic responses and major molecular responses more rapidly there was no statistical difference in the overall rates of either of these parameters with 1 year of follow-up.[10]

The measurement of trough levels of imatinib is not, at present, a mandatory standard of care. There are, however, several retrospective studies which suggest trough imatinib levels are predictive of response in imatinib-treated CML patients. Picard *et al.*[11] found trough imatinib plasma levels ranging from 181 to 2947 ng/mL in 68 French patients taking 400 mg to 600 mg of imatinib once daily. Trough imatinib levels were found to correlate with the achievement of major molecular response with patients achieving trough imatinib levels of >1002 ng/mL being significantly more likely to achieve a major molecular response [odds ratio (OR) 7.80; 95% confidence interval (95% CI) 2.64-23.03; $P<0.001$].[11] In studies performed on the IRIS trial a clear relationship was observed between trough imatinib levels, and the likelihood of achieving complete cytogenetic response and major molecular response. Trough imatinib levels in this study were assessed based on quartiles in which quartile 1 was the lowest, and quartiles 2 and 3 were grouped together. Of the 351 evaluable patients, a total of 297 achieved a complete cytogenetic response (84.6%): 66 (75.9%) in quartile 1; 152 (85.4%) in quartiles 2 and 3; and 79 (91.9%) in quartile 4 ($P=0.01$).[12] These studies suggest that trough imatinib levels provide a good indicator of outcome in imatinib-treated patients and, furthermore, that these levels provide a more reliable predictor than Sokal score.[13] To date, however, no other prognostic markers have been assessed in combination with trough imatinib levels.

This current study of patients enrolled in the TOPS trial provides the opportunity to assess the predictive value of OCT-1 activity in an independent cohort of patients. In addition, we assessed the impact of standard-dose imatinib (400 mg/day) and high-dose imatinib (800 mg/day) on molecular response in patients with low OCT-1 activity and the predictive value of OCT-1 activity in combination with trough imatinib plasma levels.

Design and Methods

Patients' samples

For this study blood was available from 100 CP-CML patients enrolled in the TOPS study. The inclusion of patients in this study was based solely on sample availability, and no additional selection criteria were applied. The baseline characteristics and dosing demographics of this group of patients were comparable to those of all patients enrolled in the TOPS study (*Online Supplementary Tables S1 and S2*)[14] TOPS was a phase III multicenter study in which patients were assigned to imatinib 800 mg/day or 400 mg/day. Patients were stratified according to Sokal score at diagnosis.[13] Samples were collected from Australia, Italy, Korea and the USA. All studies were approved by institutional human research ethics committees and all samples were collected with informed consent, in accordance with the Declaration of Helsinki. Importantly, all baseline samples were collected prior to the commencement of imatinib therapy. OCT-1 activity was determined at baseline and trough levels of imatinib in the plasma were assayed after 12 months of imatinib treatment. In this cohort, 28/100 patients had been randomly assigned to the 400 mg/day arm, the remaining 72 patients to the 800 mg/day arm.

Radiolabeled drug uptake and determination of OCT-1 activity

Imatinib mesylate (Glivec; Novartis Pharmaceuticals, Basel, Switzerland), together with ^{14}C-imatinib were kindly provided by Novartis Pharmaceuticals. The intracellular uptake and retention assay was performed, as previously described, on cryopreserved blood mononuclear cell.[6,15,16] OCT-1 activity is defined as the difference between intracellular uptake and retention in the absence and in the presence of the potent OCT-1 inhibitor prazosin.[17]

Imatinib therapeutic drug monitoring

Trough imatinib levels were measured by Novartis Pharmaceuticals. For this analysis, blood samples were collected from 100 patients prior to the morning imatinib dose, following 12 months of imatinib therapy. Plasma concentrations of imatinib were measured using liquid chromatography and tandem mass spectrometry with deuterated imatinib as the internal standard.

Response criteria

The molecular response, as determined by real-time quantitative reverse transcriptase polymerase chain reaction (RQ-PCR) for *BCR-ABL*, was used to compare outcomes between groups during the course of the study for each patient. A major molecular response was defined as a *BCR-ABL* level ≤0.1% on the international scale. The definition of failure of imatinib therapy was that in the *LeukemiaNET* Guidelines 2009.[18]

Statistics

All statistical analyses were performed using Sigma Stat Software

(Systat, San Jose, CA, USA). Efficacy analyses for overall outcomes and the effect of different dosages were performed on the intent-to-treat population. Time to response and overall response were analyzed using the Kaplan-Meier method, and treatment differences were assessed using the log-rank test. The t-test and ranks sum test were used to define differences between groups as appropriate and the odds ratio test was used to determine the significant effect of dose and OCT-1 activity as single variables.

Results

Randomized dose and the achievement of a major molecular response by 24 months

In this study the median duration of imatinib exposure was 24 months (range, 12-24 months). There was no significant difference in the duration of exposure to imatinib between the patients in the 400 mg/day and 800 mg/day arms (P=0.460). Patients were divided into those randomized to 400 mg/day (n=28) and those to 800 mg/day (n=72) and their achievement of major molecular response by 24 months was assessed. The results in this cohort of 100 patients reflected those of the overall trial, with no significant difference in the achievement of major molecular response observed at 24 months (400 mg/day, 79%; 800 mg/day, 75%; P=0.578. OR=0.818, 95% CI 0.287 to 2.385; P=0.909). As also observed in the overall trial, the median time to achieve major molecular response was slightly quicker in the 800 mg/day cohort (9 months) than in the 400 mg/day cohort (12 months), but by 24 months this difference was no longer apparent (Figure 1A) (*Online Supplementary Table S3*).

OCT-1 activity and the achievement of major molecular response by 24 months

Patients were grouped according to whether they had low OCT-1 activity (n=67) or high OCT-1 activity (n=33) on the basis of the previously defined OCT-1 activity threshold level of 7.2 ng/200,000 cells.[6] In this study OCT-1 activity was predictive of the achievement of major molecular response by 24 months, irrespectively of whether patients received imatinib 400 mg/day or 800 mg/day. A significantly greater proportion of patients with high OCT-1 activity achieved a major molecular response by 24 months [66% (44/67) of patients with low OCT-1 activity *versus* 97% (32/33) of patients with high OCT-1 activity; P<0.001. OR=0.0598, 95% CI 0.00767 to 0.466; P<0.001] (Figure 1B).

Limiting the analysis to those patients randomized to imatinib 400 mg/day revealed that a significantly greater proportion of patients with high OCT-1 activity (n=14) achieved a major molecular response by 24 months when compared to patients with low OCT-1 activity (n=14) (low OCT-1 activity, 57%; high OCT-1 activity, 100%; P<0.001) (Figure 2A). In patients randomized to imatinib 800 mg/day (n=72) again a greater proportion of patients with high OCT-1 activity achieved a major molecular response when compared to patients with low OCT-1 activity, but the difference in proportions failed to reach statistical significance [low OCT-1 activity, 68% (n=53): high OCT-1 activity, 95% (n=19) P=0.073] (Figure 2B).

Examining the rate of response in patients with high OCT-1 activity revealed that 50% of those patients who achieved a major molecular response did so by 9 months regardless of dose. In contrast, among the group with low OCT-1 activity, higher dose had a significant impact on the rate of response with 50% of patients who achieved a major molecular response on 400 mg/day doing so by 18 months compared to 9 months among the patients on 800 mg/day (Figure 2A and B).

Trough imatinib levels, OCT-1 activity and response

The mean ± standard deviation (SD) trough imatinib

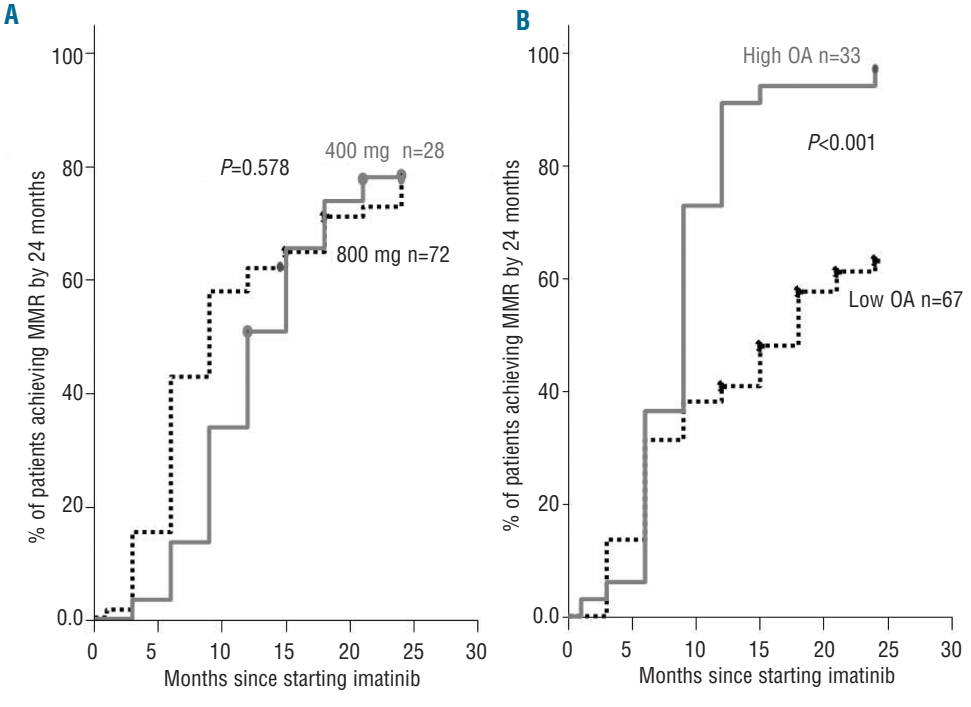

Figure 1. The proportion of patients achieving major molecular response (MMR) by 24 months based on (A) patients randomized to 400 mg/day and 800 mg/day, and (B) based on high and low OCTT-1 activity (OA). Kaplan Meier analysis demonstrate there that was no significant difference in the achievement of MMR between patients treated with imatinib 400 mg/day or 800 mg/day; however there was a significantly higher rate of MMR in patients with high OA than in those with low OA (P<0.001).

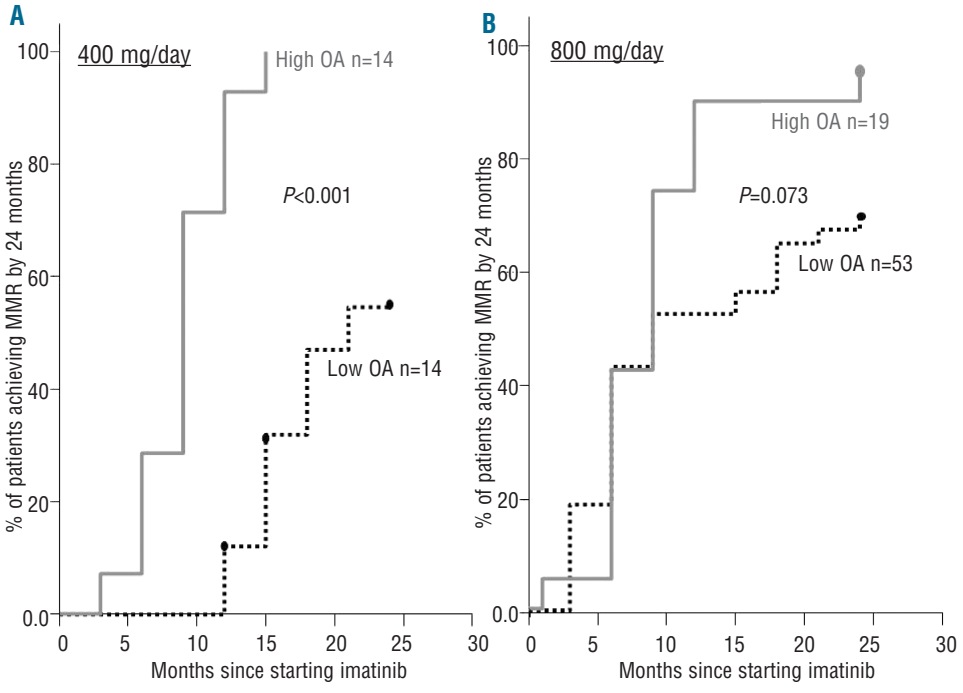

Figure 2. The effect of randomized imatinib dose [400 mg (A) and 800 mg (B)] on the achievement of major molecular response (MMR) by 24 months in patients grouped into those with low and those with high OA. Kaplan-Meier analysis revealed a significant difference between low and high OA curves in patients randomized to 400 mg/day, but this difference was abrogated in patients treated with 800 mg/day. In addition, while the rate of response (time to achieve MMR) in patients with high OA was similar whether the patient was treated with 400 mg or 800 mg, in patients with low OA the rate of response was much faster in patients treated with 800 mg than in those treated with 400 mg.

level at 12 months in this cohort of 100 patients was 1943 ng/mL ± 1027 (median, 1685 ng/mL; range, 0 to 4200 ng/mL). In patients randomized to 400 mg/day the mean ± SD was 1416 ± 847 ng/mL (median, 1250 ng/mL; range, 0 to 3940 ng/mL), which was significantly lower than that observed in the 800 mg/day cohort (2164 ± 1068 ng/mL; median, 1980 ng/mL; range, 149 to 4960 ng/mL; $P<0.001$).

Investigation of the trough imatinib plasma levels in patients with low OCT-1 activity revealed that the achievement of major molecular response was associated with a significantly higher imatinib level than that observed in patients who failed to achieve a major molecular response (median 1890 ng/mL *versus* 1455 ng/mL, respectively $P=0.034$) (Figure 3). In patients with high OCT-1 activity who achieved a major molecular response the median trough imatinib level was 1630 ng/mL which was not significantly different from that in either the low OCT-1 activity group (low OCT-1 activity with major molecular response: $P=0.288$; low OCT-1 activity without major molecular response: $P=0.285$).

The trough imatinib plasma levels at 12 months were divided into quartiles and the effect of each quartile on the achievement of major molecular response was assessed. A lower proportion of patients with plasma levels <1200 ng/mL (quartile 1) achieved a major molecular response by 24 months (Table 1).

Assessing the impact of imatinib plasma levels on the achievement of major molecular response in patients with low and high OCT-1 activity revealed that patients with low OCT-1 activity and trough imatinib levels <1200 ng/mL (quartile 1) had significantly lower rates of major molecular response than all other groups [low OCT-1 activity, quartile 1 imatinib trough level, 47% (n=15) *versus* all other patients, 81% (n=85); $P=0.009$]. Importantly there was a significant difference between the low and high OCT-1 activity groups in the percentage of patients achieving major molecular response in quartile 1 (47% *versus* 90%; $P=0.007$), but no significant difference between these two groups when considering quartile 2, 3 or 4 (Table 1) (Figure 4B and C), although the numbers in each group were small.

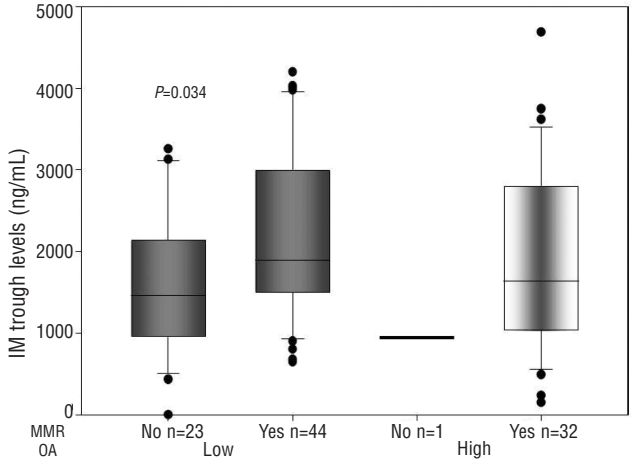

Figure 3. Box plot showing the median and range of trough imatinib plasma levels measured following 12 months of therapy in patients who did or did not achieve a major molecular response (MMR) within the group with low or high OCT-1 activity (OA). Focusing only on the low OA group reveals that the 12-month imatinib plasma level was significantly higher in patients achieving a MMR than in those who failed to achieve a MMR.

Imatinib failure

While the overall rate of progressive disease in the TOPS study over the first 18 months was reported to be 11/476 (2.3%) no patients with accelerated phase or blast crisis were among the patients studied in the current cohort of patients. Imatinib treatment failed, as defined by the ELN criteria,[18] in 14 of the 100 patients in this study. One patient developed mutations within the kinase

domain (Y253H and T315I) at 9 months, four patients failed to achieve a complete hematologic response at 3 months, five failed to achieve a complete cytogenetic response by 18 months and the remaining four patients lost a complete cytogenetic response (at 9, 12, 15 and 18 months). Thirteen of these 14 patients had low OCT-1 activity, including the patient who developed mutations. There was a significant difference between the groups with low and high OCT-1 activity with respect to imatinib failure (low OCT-1 activity, 19%; high OCT-1 activity, 3%; *P*=0.029) (Figure 5A). Seven of the 14 patients in whom imatinib failed had trough imatinib levels in the lowest quartile, with three patients in quartile 2, three in quartile 3 and one in quartile 4.

Focusing only on patients with low OCT-1 activity, a significant difference was found in the rate of imatinib failure between those with trough imatinib levels in quartile 1 and those in all other quartiles [low OCT-1 activity, quartile 1 trough level 40% (n=15); other quartiles 13% (n=52); *P*=0.014]. There was no significant effect of trough imatinib levels in patients with high OCT-1 activity [quartile 1 trough level, 10% (n=10); other quartiles, 0% (n=23); *P*=0.138)] (Figure 5B and C). Similarly, limiting the analysis to those patients randomized to imatinib 400 mg/day revealed a significant difference in the percentages of patients in whom imatinib failed between those with low OCT-1 activity and those with high OCT-1 activity [low OCT-1 activity, 29% (n=14) *versus* high OCT-1 activity, 0% (n=53); *P*=0.034]. In those randomized to 800 mg/day, the difference was no longer statistically significant [low OCT-1 activity, 17% (n=14) *versus* high OCT-1 activity, 5% (n=19); *P*=0.209] indicating the impact of dose.

Table 1. The percentage of patients achieving a major molecular response (MMR) by 24 months based on trough imatinib plasma levels (divided into quartiles) following 12 months of imatinib therapy.

Imatinib plasma level (ng/mL)	% of patients achieving MMR by 24 months (n) Total	Low OCT-1 activity	High OCT-1 activity	*P* value
Quartile 1 (<1200)	64 (25)	47 (15)	90 (10)	0.007
Quartile 2 (≥1200)	80 (25)	71 (17)	100 (8)	0.064
Quartile 3 (≥1700)	76 (25)	68 (19)	100 (6)	0.081
Quartile 4 (≥2800)	84 (25)	75 (16)	100 (9)	0.396

Importantly, comparing the rate of imatinib failure in the low OCT-1 activity quartile 1 trough level cohort of patients with all other patients demonstrated that this cohort of patients are at the highest risk of imatinib failure [low OCT-1 activity, quartile 1 imatinib trough levels, 40% (n=15) *versus* all other patients, 9% (n=85); *P*<0.001]. These data again highlight the importance of dose and high imatinib trough levels in patients with low OCT-1 activity.

Discussion

The suggestion from several earlier non-randomized studies[9,19-22] that higher imatinib doses may result in improved responses in CP-CML patients treated with imatinib was not supported by the overall analysis of the TOPS study.[10] Patients treated with 800 mg/day achieved complete cytogenetic response and major molecular

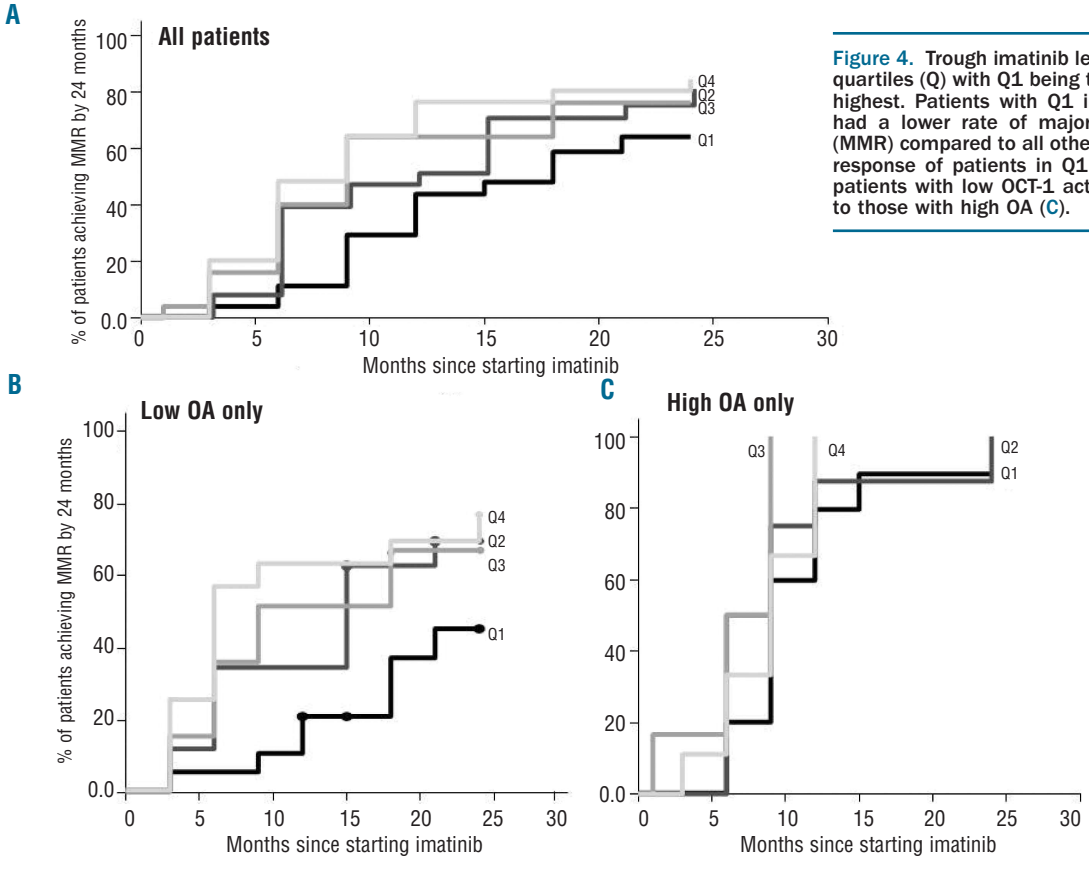

Figure 4. Trough imatinib levels were divided into quartiles (Q) with Q1 being the lowest and Q4 the highest. Patients with Q1 imatinib trough levels had a lower rate of major molecular response (MMR) compared to all other groups (A). The poor response of patients in Q1 can be attributed to patients with low OCT-1 activity (OA) (B), but not to those with high OA (C).

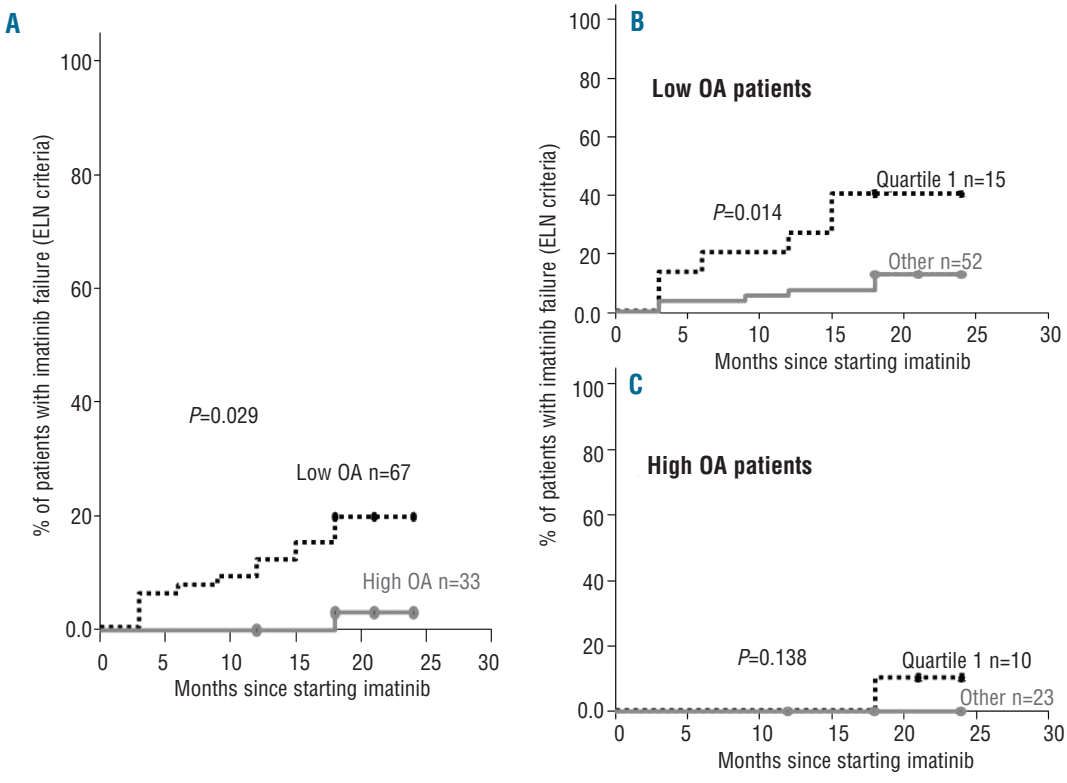

Figure 5. Assessment of imatinib failure (ELN criteria) in the setting of OCT-1 activity (OA) and trough imatinib levels in the overall cohort of patients (A), and in those with low (B) and high (C) OA. The impact of low trough imatinib levels (quartile 1) was significant in patients with low OA, but not in patients with high OA.

response more rapidly than those treated with 400 mg/day, but by 12 months there was no significant difference in the achievement of major molecular response between the two groups. While the follow-up of this study is relatively short, these data provide little support for higher dosing regimens in the setting of newly diagnosed CP-CML and substantiates initial recommendations that imatinib 400 mg/day be implemented as the standard of care for CP-CML patients.[23] The findings of this current study do, however, provide strong evidence that 800 mg/day will lead to a significantly higher rate of major molecular responses in the CP-CML setting, when considering the cohort of patients with low OCT-1 activity.

Our previous studies in the TIDEL I trial demonstrated that OCT-1 activity is an excellent predictor of both short-term and longer-term molecular response, and that patients with low OCT-1 activity have significantly inferior rates of major molecular response and complete molecular response at 24 and 60 months.[6,16] In addition, patients with low OCT-1 activity have the lowest event-free and transformation-free survival rates at 5 years. These results were found in the setting of CP-CML patients treated with the higher dosing regimen of 600 mg/day imatinib as front-line therapy. Patients with low OCT-1 activity who were unable to tolerate this regimen over the first 12 months of treatment and, therefore, received an average daily dose of <600 mg, had significantly poorer responses overall (achievement of major molecular response, event-free and transformation-free survival) compared to patients receiving 600 mg/day.[16] While these data suggest that OCT-1 activity could be used to guide imatinib dose selection, the findings related to the impact of lower dose from TIDEL-I were in a setting of patients intolerant to 600 mg imatinib hence, variable dosing, including dose interruptions, may have contributed to the relationship we described. We and others[10] have previously demonstrated that dose interruptions over the first 12 months of therapy negatively affect outcome.[9] The predictive value of OCT-1 activity has not previously been examined in patients assigned to a randomized dose of either 400 mg/day or 800 mg/day.

The results reported in this current study from patients enrolled in the TOPS trial validate and extend our previous findings and demonstrate, in an independent cohort, that OCT-1 activity is predictive of molecular response after 24 months of imatinib therapy, and that patients with low OCT-1 activity are at the greatest risk of sub-optimal response and imatinib failure. Here, for the first time we provide evidence that patients with low OCT-1 activity achieve significantly better responses on 800 mg/day than those on 400 mg/day, and importantly that patients with high OCT-1 activity achieve excellent responses on either 400 mg/day or 800 mg/day, suggesting that higher dosing regimens are of no clinical benefit for these patients.

The TOPS study has provided the opportunity to assess the impact of OCT-1 activity in relation to trough imatinib plasma levels in patients treated daily with either 400 mg or 800 mg imatinib. In keeping with the findings of Larson we found that patients with pharmacokinetic levels in the lowest quartile had the lowest rates of major molecular response overall, suggesting that low drug exposure negatively affects outcome in patients treated with imatinib. However, this relationship was only evident for patients with low OCT-1 activity who had trough imatinib plasma levels in the lowest quartile for this study (<1200 ng/mL). These patients were at the highest risk of failing to achieve a major molecular response and of imatinib failure. Importantly it was almost exclusively these patients with

low OCT-1 activity who contributed to the poor response observed in the cohort of patients with imatinib levels in the lowest pharmacokinetic quartile (<1200 ng/mL), suggesting that in patients with high OCT-1 activity, a drug level <1200 ng/mL does not predict an inferior molecular response. These are clinically important findings now that monitoring of imatinib drug levels is globally available. Finally this study demonstrated that OCT-1 activity could be successfully measured in Australia in samples collected and cryopreserved across four continents before being shipped to this country.

In summary, in patients with low OCT-1 activity a trough plasma level of imatinib below 1200 ng/mL is clearly associated with an inferior response and a higher risk of imatinib failure, and higher trough imatinib levels may be needed to improve the rate of major molecular responses and reduce the risk of treatment failure in these patients. In patients with high OCT-1 activity the trough imatinib threshold is likely to be much lower, but cannot be determined in this study given the excellent molecular response of 97% of patients in this group. Indeed we found no evidence to suggest that therapeutic imatinib monitoring is of any clinical value in patients with high OCT-1 activity. This is the first study, to our knowledge, which addresses trough imatinib monitoring in the setting of other response predictors.

In conclusion, this study provides a strong therapeutic rationale for the selection of imatinib dose based on OCT-1 activity in newly diagnosed CP-CML patients. Furthermore, we provide evidence for the potential clinical value of plasma trough imatinib monitoring in this setting.

In patients with low OCT-1 activity, standard-dose imatinib is not optimal, and these patients are more likely to benefit from higher dosing regimens (800 mg/day) coupled with close trough imatinib monitoring to target levels above 1200 ng/mL. Based on the recent favorable response rates observed with first-line nilotinib[24,25] and dasatinib.[25] when compared to imatinib in phase III trials these second-generation kinase inhibitors would likely be most beneficial in patients with low OCT-1 activity. If high-dose imatinib is used in this setting, intolerance and/or failure to achieve sufficient plasma levels would also be a suitable reason for the use of second-generation drugs. The transport of both of these drugs is independent of OCT-1.[15,26] In contrast, patients with high OCT-1 activity achieve excellent therapeutic responses on either dose of imatinib and there is no evidence to support the use of high-dose or second-generation therapy in this setting.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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