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Predictive value of early molecular response for deep molecular response in chronic phase of chronic myeloid leukemia

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Abstract

To investigate the association of 3- and 6-month BCR-ABL transcript levels on the international scale (BCR-ABL^{IS}) and other factors with deep molecular response (DMR) achievement in chronic myeloid leukemia (CML)-chronic phase (CP) patients receiving tyrosine kinase inhibitor (TKI) therapy.

We retrospectively analyzed the clinical data of 206 patients enrolled in our hospital between January 2010 and July 2018. These patients were initially diagnosed with CML-CP and received imatinib or nilotinib therapy. Early molecular response (EMR) was assessed based on BCR-ABL^{IS} (IS: on the international scale) transcript level at 3 and 6 months. Potential factors impacting DMR achievement were identified using Cox proportional hazard regression models. The effects of EMR achievement on the cumulative incidence of MR4.0 were investigated via Kaplan–Meier analysis.

Multivariate Cox regression analysis showed that a BCR-ABL^{IS} transcript level at 3 and 6 months of TKI therapy was an independent factor for the achievement of MR4.0, which was nevertheless not related to age, gender, Sokal score, hemoglobin level, or white blood cell (WBC) count at the initial time of diagnosis. Patients achieving an EMR (EMR: 3-month BCR-ABL^{IS} $\leq$10%, 6-month BCR-ABL^{IS} $<$1%) were more likely to reach MR4.0 than patients failing to achieve EMR ($P_1 < .001$, $P_2 < .001$). Patients who had 3-month BCR-ABL^{IS} $\leq$1% were more likely to reach MR4.0 than those who had 3-month BCR-ABL^{IS} of 1% to 10% or $>$10% ($P_1 = .001$, $P_2 < .001$). Similarly, patients who had 6-month BCR-ABL^{IS} $\leq$0.1% were more likely to achieve MR4.0 than those in the 0.1% to 1% and $\geq$1% groups ($P_1 < .001$, $P_2 < .001$). Also, a higher percentage of patients on nilotinib therapy achieved EMR compared with patients on imatinib therapy (93.3% vs 63.6% on 3-month nilotinib therapy, $P = .001$; 88.9% vs 59.9% on 6-month nilotinib therapy, $P = .004$).

This study demonstrates that EMR, especially a 3-month BCR-ABL^{IS} $\leq$1% and 6-month BCR-ABL^{IS} $\leq$0.1%, have predictive value for DMR achievement. In addition, there is a higher percentage of patients receiving nilotinib therapy achieved EMR than that of those receiving imatinib therapy.

Abbreviations: CML = chronic myeloid leukemia, CP = chronic phase, DMR = deep molecular response, EMR = early molecular response, TFR = treatment-free remission, TKI = tyrosine kinase inhibitor, WBC = white blood cell.

Keywords: chronic myeloid leukemia in chronic phase, deep molecular response, early molecular response, treatment-free remission, tyrosine kinase inhibitors

1. Introduction

Chronic myeloid leukemia (CML) is a malignant hematologic disease that arises from the pluripotent hematopoietic stem cells, with an incidence of approximately 1/100,000 and a natural course of 3 to 5 years. Imatinib, as the first-generation tyrosine kinase inhibitor (TKI), has been extensively used for the treatment of CML in the chronic phase (CP) and has effectively prolonged the survival time of CML-CP patients with an average 10-year overall survival rate of 83.3%. Thus, this TKI therapy has transformed CML from an incurable malignancy into a manageable chronic disease, giving patients a normal life span with the use of only oral medicines.[1,2] Currently, some portion of CML-CP patients who have achieved a stable deep molecular response (DMR) on long-term TKI therapy can attempt to stop TKI therapy. In the first multicenter prospective trial, the Stop Imatinib study (STIM), 100 CML-CP patients who had received imatinib therapy for $\geq$3 years and had maintained undetectable minimal residual disease ($>$5-log reduction in BCR-ABL and ABL transcript levels with undetectable levels on quantitative RT-PCR) for $\geq$2 years stopped imatinib therapy. 24 months after imatinib discontinuation, 39 of these patients still had undetectable BCR-ABL transcript levels. Thus, the rate of treatment-free remission (TFR) was 39% (95% confidence interval [CI] 29%–48%), and importantly, these patients were able to maintain molecular remission without further imatinib therapy.[3–7] TFR is becoming a potential ultimate goal of CML-CP treatment. Although the optimal durations of TKI therapy and DMR before TKI discontinuation remain under debate, achievement of MR4.0 is a minimum requirement for effective TKI treatment

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of CML-CP.[8–12] Therefore, it is important to identify the factors that contribute to MR4.0 achievement in order to enable more CML-CP patients to reach the threshold for TKI discontinuation.

According to the guidelines issued by the European LeukemiaNet (ELN), BCR-ABL transcript levels on the international scale (BCR-ABL^{IS}) at 3 and 6 months are defined as indicators of the early efficacy of first-line TKI treatment. A BCR-ABL^{IS} $\leq$10% after 3 months of TKI treatment or BCR-ABL^{IS} <1% after 6 months of treatment indicates an optimal response to TKI therapy with no need to adjust the therapeutic strategy. Early molecular response (EMR) achievement has been shown to correlate with good prognosis, including improved long-term overall survival (OS) and progression-free survival (PFS) and a lower transformation rate to accelerated/blast phases in CML-CP patients.[13–20] However, little is known about the relationship between EMR and DMR in CML-CP patients receiving TKI treatment or other factors that contribute to the achievement of DMR. We conducted the present retrospective analysis of CML-CP patients treated at our hospital to address these issues.

2. Methods

The study population comprised 206 CML-CP patients who received TKI therapy in our hospital between January 2010 and July 2018. These patients were diagnosed according to the 2016 World Health Organization (WHO) criteria,[21] treated with a TKI within 1 year of diagnosis and for at least 6 months (3-month or 6-month molecular data were available), and serially monitored in our hospital. Patients who switched from imatinib to nilotinib therapy during treatment were excluded.

Based on ELN recommendations for the management of adult CML-CP, patients were treated with imatinib or nilotinib,[13] according to multiple factors including risk score, comorbidities, chromosomal karyotype, and patients' willingness. Cytogenetic monitoring (Giemsa banding) was performed at 3, 6, 12, and 18 months after diagnosis and the start of treatment, and once per year in patients who achieved a complete cytogenetic response (CCyR). Molecular monitoring (real-time quantitative reverse-transcription polymerase chain reaction, qRT-PCR) using peripheral blood samples was performed at 3 and 6 months and repeated every 3 to 6 months. Molecular response (MR)4.0 was defined as 0.0032%< BCR-ABL^{IS} $\leq$0.01% (ABL1 transcripts $\geq$10 000), MR4.5 as 0.001% <BCR-ABL^{IS} $\leq$0.0032% (ABL1 transcripts $\geq$32 000), and MR5.0 as BCR-ABL^{IS} $\leq$0.001% (ABL1 transcripts $\geq$100 000). DMR was defined by $\geq$MR4.0,[22] The protocol followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the First Hospital of Jilin University. Informed consent was obtained from all participants.

SPSS software for Windows version 23.0 (SPSS Inc, Chicago, IL) was used for statistical analysis. Data that followed a normal distribution are presented as mean $\pm$ standard deviation (SD). Data that followed a skewed distribution are expressed as the median (P_{25}, P_{75}) (P: percentile). Data were compared between 2 groups using Pearson χ^2 test or Fisher exact test. A P value <.05 was considered statistically significant. Kaplan–Meier analysis was used to assess the cumulative incidence of MR4.0, which was compared between groups using the log-rank test and among multiple groups with a combination of log-rank test and Bonferroni correction. For this analysis, a P value <.0167 was considered statistically significant. A multivariate Cox proportional hazards regression analysis was performed by inputting the single variables for which P <.2.

Table 1

Baseline characteristics of study population.

Characteristic	Receiving TKI treatment (n = 206)
Imatinib, n (%)	173 (84.0)
Nilotinib, n (%)	33 (16.0)
Male, n (%)	137 (66.5)
Median age (25th–75th percentile), years	42 (30–51)
Median follow-up time (25th–75th percentile), months	27 (16–50)
Sokal risk group, n (%)	
Low	87 (42.2)
Intermediate	54 (26.2)
High	31 (15.0)
Missing*	34 (16.5)
Median white-cell count (25th–75th percentile) ($\times 10^9$/L)	176.2 (84.8–291.6)
Median platelet count (25th–75th percentile) ($\times 10^9$/L)	399.0 (267.0–628.5)
Median hemoglobin count (25th–75th percentile) (g/L)	107.0 (93.0–119.5)

TKI = tyrosine kinase inhibitor.

* Sokal risk scores could not be calculated for patients with missing data for baseline parameters required for the calculation of these scores.

3. Results

3.1. Characteristics of the study population

Among the 206 patients enrolled in the present study, 173 patients received first-line imatinib therapy with the starting dose of 400 mg QD, and 33 patients received first-line nilotinib therapy with the starting dose of 300 mg BID. The baseline patient characteristics are presented in Table 1.

3.2. Assessment of therapeutic response to TKI at 3 and 6 months

The following results were obtained from the data of 162 of the 206 patients who were subjected to 3-month molecular monitoring and 164 of the 206 patients who were subjected to 6-month molecular monitoring. The results showed that 69.1% (112/162) of CML-CP patients had a BCR-ABL^{IS} transcript level $\leq$10% after 3 months of imatinib or nilotinib therapy. Specifically, 63.6% (84/132) of patients receiving imatinib had a BCR-ABL^{IS} $\leq$10%, and this percentage was increased to 93.3% (28/30) in patients who received nilotinib (P = .001 vs imatinib; Fig. 1A), suggesting that TKI therapies allow the majority of CMP-CP patients to achieve an EMR with nilotinib having greater therapeutic value than imatinib. This observation was further confirmed by the data for a 3-month BCR-ABL^{IS} $\leq$1% (21.2% on imatinib vs 60.0% on nilotinib, P <.001). Furthermore, after 6 months of imatinib or nilotinib therapy, the BCR-ABL^{IS} levels were less than 1% in 64.6% (106/164) of patients (59.9% on imatinib vs 88.9% on nilotinib, P = .004; Fig. 1B) and less than 0.1% in 26.8% (44/164) of patients (24.1% on imatinib vs 40.7% on nilotinib, P = .074). Collectively, these results indicate that imatinib and nilotinib contribute to the achievement of EMR in CML-CP patients, and nilotinib appears to be generally more effective at treating CML-CP than imatinib.

3.3. Prognostic value of the 3-month BCR-ABL^{IS} transcript level

As shown in Figure 2A, patients who had a 3-month BCR-ABL^{IS} $\leq$10% had a significantly superior cumulative incidence of MR4.0 than those who had a BCR-ABL^{IS} >10% (P <.001). The

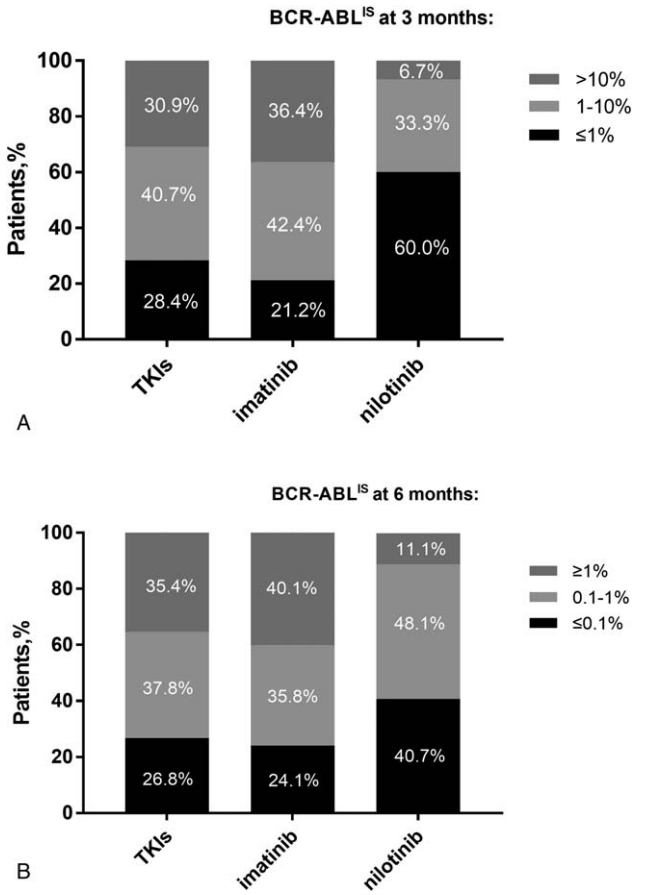

Figure 1. Distributions of CML-CP patients who had different BCR-ABL^{IS} transcript levels at 3 months (A) and 6 months (B) on imatinib or nilotinib therapy. Patients with unevaluable or missing PCR assessments were excluded from the study. CML = chronic myeloid leukemia, CP = chronic phase, PCR = polymerase chain reaction.

median follow-up time was 27 months. EMR means quicker achievement of MR4.0, and the median time was 39 months (95% CI: 30.6–47.4 months). In patients who achieved an EMR, the percentage of patients who achieved MR4.0 by 48 months was 62.2% (95% CI: 47.4%–77.0%). In patients who did not to achieve an EMR, the median time to MR4.0 could not be calculated (not reached), and the percentage of the patients who had achieved MR4.0 at 48 months was only 18.3% (95% CI: 6.4%–46.0%). In addition, we also found no significant difference in the cumulative incidence of MR4.0 between patients who had BCR-ABL^{IS} >10% and those who had 1% <BCR-ABL^{IS} ≤10% ($P = .023$) by Kaplan–Meier analysis. However, the difference in the incidence of MR4.0 was statistically significant between those with BCR-ABL^{IS} ≤1% and those with BCR-ABL^{IS} >10% and between those with BCR-ABL^{IS} ≤1% and those with 1% <BCR-ABL^{IS} ≤10% ($P < .001$ and $P = .001$, respectively). According to 2-year, 3-year, and 4-year cumulative incidences of MR4.0, patients who had BCR-ABL^{IS} ≤1% were more likely to achieve MR4.0 than those who had 1% <BCR-ABL^{IS} ≤10% or BCR-ABL^{IS} >10% (Table 4). These data demonstrate that a DMR may be achieved more quickly in patients who have a 3-month BCR-ABL^{IS} ≤1%.

We next sought to identify the baseline risk factors for the achievement of MR4.0. By univariate Cox regression analysis of baseline variables including age, gender, hemoglobin level, white blood cell (WBC) count, and platelet (PLT) count at diagnosis, we identified the variables for which $P < .2$, and these included gender, WBC count, PLT count, and hemoglobin level. Then we performed a multivariate analysis of 3-month BCR-ABL^{IS} level, Sokal score, gender, PLT count, WBC count, and hemoglobin level and found that the 3-month BCR-ABL^{IS} level and PLT count correlated with the achievement of MR4.0 ($P = .001$ and $P = .021$, respectively; Table 2). The results demonstrated that the 3-month BCR-ABL^{IS} transcript level was an independent predictive factor of achievement of MR4.0. Consistently, the probability of achieving MR4.0 was 71.5% lower in patients who had 1% <3-month BCR-ABL^{IS} ≤10% than in those who had a 3-month BCR-ABL^{IS} ≤1% (hazard ratio [HR] = 0.285, 95% CI: 0.109–0.747, $P = .011$), and the probability of reaching MR4.0 was decreased by 90.5% in patients who had a 3-month BCR-ABL^{IS} >10% (HR = 0.095, 95% CI: 0.024–0.377, $P = .001$). These results suggest that patients who have a 3-month BCR-ABL^{IS} ≤1% have a higher possibility of achieving a DMR.

3.4. Prognostic value of the 6-month BCR-ABL^{IS} transcript level

In accordance with the data for the 3-month BCR-ABL^{IS}, patients who had a 6-month BCR-ABL^{IS} <1% had a much higher cumulative incidence of MR4.0 than those who had a BCR-ABL^{IS} ≥1% ($P < .001$; Fig. 2C), with the median time to MR4.0 of 39 months (95% CI: 27.8–50.2 months). The percentage of these patients who had achieved MR4.0 by 48 months was 65.9% (95% CI: 51.0%–81.1%). For the patients who did not achieve an EMR, the median time to MR4.0 could not be calculated (not reached), and the percentage of these patients who had achieved MR4.0 by 48 months was as low as 18.6% (95% CI: 6.6%–46.4%).

Furthermore, patients who had a BCR-ABL^{IS} ≤0.1% had a higher cumulative incidence of MR4.0 than those who had a BCR-ABL^{IS} ≥1% or 0.1%< BCR-ABL^{IS} <1% ($P < .001$ and $P < .001$, respectively), which was consistent with the data for the 2-year, 3-year, and 4-year cumulative incidences of MR4.0 (Fig. 2D and Table 4). Taken together, these data suggest that MR4.0 was achieved more quickly by patients who had a BCR-ABL^{IS} ≤0.1%. Moreover, the cumulative incidence of MR4.0 differed significantly between the BCR-ABL^{IS} ≥1% and 0.1%< BCR-ABL^{IS} <1% groups ($P = .003$), suggesting that patients who have a 6-month BCR-ABL^{IS} ≥1% have the lowest probability of achieving a DMR.

According to multivariate Cox regression analysis, the 6-month BCR-ABL^{IS} level and PLT count at the initial time of diagnosis correlated with the achievement of MR4.0 ($P < .001$ and $P = .002$, respectively; Table 3), suggesting that the 6-month BCR-ABL^{IS} transcript level is an independent predictive factor for the achievement of MR4.0. Similar to the data for 3-month BCR-ABL^{IS} mentioned above, a 0.1% <6-month BCR-ABL^{IS} <1% and 6-month BCR-ABL^{IS} ≥1% corresponded to probabilities of achieving MR4.0 that were 85.3% less and 94.4% less than that for a 6-month BCR-ABL^{IS} ≤0.1% (HR = 0.147, 95% CI: 0.056–0.387, $P < .001$ and HR = 0.056, 95% CI: 0.016–0.196, $P < .001$, respectively). Collectively, these results show that an EMR, especially a 3-month BCR-ABL^{IS} ≤1% or 6-month BCR-ABL^{IS} ≤0.1%), has predictive value for DMR achievement, suggesting a better prognosis in CML-CP patients treated with TKIs.

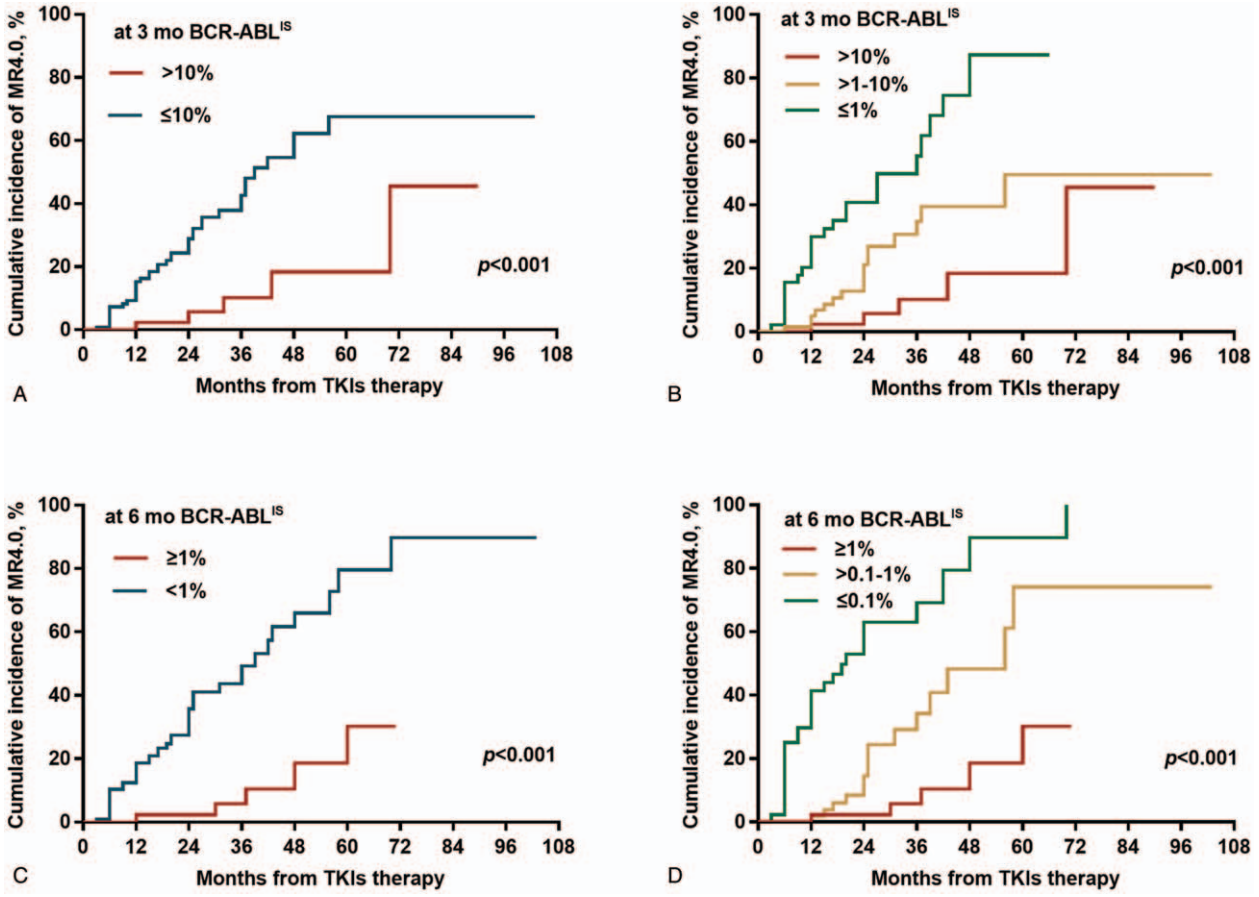

Figure 2. Cumulative incidence of MR4.0 according to BCR-ABL^{IS} transcript levels at 3 months (A and B) and 6 months (C and D) of TKI treatment. *P < .001, comparison among 3 groups. TKI = tyrosine kinase inhibitor.

4. Discussion

In the present study, we selected MR4.0 as the primary endpoint for evaluating DMR achievement for 2 reasons:

1) to ensure the validity and reliability of the data, although specificity of qRT-PCR assays in our hospital lab (a nationally standardized lab) could reach MR4.5 for DMR and MR5.0 for UMRD (our future study will be based on MR4.5 or MR 5.0 achievement, if our lab is approved for international standardization by the International Accreditation Council); and
2) to meet the eligibility criterion for TKI cessation.

These relatively lenient criteria may allow more CML-CP patients to achieve TFR in the future. The European Stop TKI

Table 2

Results of Cox multivariable regression analyses for potential factors associated with the incidence of MR4.0.

Variable	HR	95% CI	*P*
BCR-ABL^{IS} at 3 months			.001
≤1%	Reference		
1%–10%	0.285	0.109–0.747	.011
>10%	0.095	0.024–0.377	.001
WBC	0.996	0.992–1.001	.095
HB	0.980	0.959–1.001	.060
Gender	1.447	0.612–3.419	.400
Sokal risk group			.444
Low	2.034	0.441–9.373	.362
Intermediate	1.308	0.248–6.887	.751
High	Reference		
PLT	1.001	1.000–1.002	.021

HB = hemaglobin, PLT = platelet, WBC = white blood cell.

Table 3

Results of Cox multivariable regression analyses for potential factors associated with the incidence of MR4.0.

Variable	HR	95% CI	*P*
BCR-ABL^{IS} at 6 months			<.001
≤0.1%	Reference		
0.1%–1%	0.147	0.056–0.387	<.001
≥1%	0.056	0.016–0.196	<.001
WBC	0.998	0.994–1.003	.435
HB	0.982	0.959–1.006	.136
Gender	0.913	0.397–2.095	.829
Sokal risk group			.385
Low	2.081	0.597–7.254	.250
Intermediate	1.303	0.325–5.226	.709
High	Reference		
PLT	1.001	1.000–1.002	.002

HB = hemaglobin, PLT = platelet, WBC = white blood cell.

Table 4

Cumulative incidence of MR4.0 according to BCR-ABL^{IS} at 3 and 6 months.

Group	0 Month No. at risk	Median time (Mo)	24 Months		36 Months		48 Months	
			%	95% CI	%	95% CI	%	95% CI
BCR-ABL^{IS} at 3 months								
>10%	50	–	5.7	1.4 to 21.4	10.2	3.2 to 29.4	18.3	6.4 to 46.0
≤10%	112	39	28.9	20.6 to 39.5	42.7	31.7 to 55.6	62.2	47.4 to 77.0
BCR-ABL^{IS} at 3 months								
>10%	50	–	5.7	1.4 to 21.4	10.2	3.2 to 29.4	18.3	6.4 to 46.0
1%–10%	66	–	21.2	11.8 to 36.6	34.8	21.4 to 53.1	39.4	24.8 to 58.7
≤1%	46	36	40.7	27.4 to 57.3	55.4	38.3 to 74.1	87.3	67.6 to 97.7
BCR-ABL^{IS} at 6 months								
≥1%	58	–	2.3	0.3 to 15.1	5.8	1.4 to 21.8	18.6	6.6 to 46.4
<1	106	39	35.7	26.2 to 47.3	49.2	37.2 to 62.8	65.9	51.0 to 81.1
BCR-ABL^{IS} at 6 months								
≥1%	58	–	2.3	0.3 to 15.1	5.8	1.4 to 21.8	18.6	6.6 to 46.4
0.1%–1%	62	56	14.6	6.7 to 30.1	34.2	19.7 to 55.0	48.2	29.0 to 72.7
≤0.1%	44	20	63.0	47.5 to 78.4	69.2	51.9 to 84.9	89.7	66.0 to 99.2

CI = confidence interval.

trial (EURO-SKI, a clinical trial based on MR4.0 achievement as a criterion of TFR) reported the molecular recurrence-free survival (MRFS) rate was 52% (95% CI: 48%–56%) at 24 months after TKI discontinuation, which means that half of CML-CP patients may resume a normal lifestyle without experiencing disease relapse.[23]

The therapeutic responses at 3 and 6 months are important monitoring indexes in CML-CP patients treated with first-line TKIs. Hanfstein et al found that imatinib-treated patients who had a 3-month BCR-ABL^{IS} >10% had a lower 5-year OS rate than those who had a 3-month BCR-ABL^{IS} from 1% to 10% or ≤1%. However, the 5-year OS rates did not differ significantly those with a 3-month BCR-ABL^{IS} from 1% to 10% and those with a 3-month BCR-ABL^{IS} ≤1%. On the other hand, patients who had a 6-month BCR-ABL^{IS} ≤1% had a higher 5-year OS rate than those who had a 6-month BCR-ABL^{IS} >10% or from 1% to 10%, with no difference between the latter groups,[17] which emphasizes the predictive role of the cutoffs of 10% and 1% for the 3-month BCR-ABL^{IS} and 6-month BCR-ABL^{IS}, respectively, for long-term therapeutic response to TKIs. In addition to imatinib therapy, CML-CP patients who received nilotinib therapy had an improved 4-year OS rate following achievement of EMR at 3 and 6 months.[18] Thus, with either first-line imatinib or nilotinib therapy, a 3-month BCR-ABL^{IS} ≤10%, and a 6-month BCR-ABL^{IS} <1%, representing an EMR, have been recommended by the ELN and National Comprehensive Cancer Network (NCCN) as a goal of early TKI therapy for prediction of a long-term therapeutic response to TKIs. In the new era, the CML-CP treatment strategy aims to not merely prolong the survival time of patients but also to improve their quality of life. An operational cure should be the ultimate treatment goal.

The present study investigated the correlation between an EMR and a DMR. Of importance, the highest percentage of patients who achieved a DMR was found among those who had a 3-month BCR-ABL^{IS}≤1% and 6-month BCR-ABL^{IS} ≤0.1%, suggesting that the patients who achieve a deeper molecular response during the early stage of treatment are more likely to be able to discontinue TKI therapy (Fig. 2 and Table 4). Furthermore, we found that baseline factors such as age, gender, Sokal score, hemoglobin level, and WBC count were not associated with the cumulative incidence of MR4.0 achievement.

A series of clinical trials have shown that first-line nilotinib therapy can enable more CML-CP patients to quickly achieve DMR compared with imatinib therapy.[12,15,18,24–26] As examples, in the Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients (ENESTnd) study,[15] after 5 years of nilotinib therapy (300 mg BID), 65.6% of CML-CP patients had successfully achieved MR4.0, whereas only 41.7% of CML-CP patients receiving imatinib therapy had achieved MR4.0 (P <.0001). In addition, another study reported that 9% to 15% of CML-CP patients achieved TFR after 8 years of first-line imatinib therapy,[27] in contrast to nearly 20% after 6 years of first-line nilotinib therapy.[6,28] Because our study population included many fewer cases on nilotinib therapy (only 33 cases) than in imatinib therapy, it is difficult to compare the difference in DMR achievement between those treated with nilotinib versus imatinib. However, according to the therapeutic response to imatinib or nilotinib at 3 or 6 months, we did find that:

1) 3-month therapeutic responses to TKIs were consistent with those reported in clinical trials;[12,18] e.g., EMR achievement on imatinib (63.6% vs 67.7%[18]) and EMR achievement on nilotinib (93.3% vs 97.1%[12]);
2) nilotinib therapy allowed a significantly high percentage of CML-CP patients to achieve EMR compared with imatinib therapy (3-month EMR: 93.3% vs 63.6%, P_1 = .001; 6-month EMR: 88.9% vs 59.9%, P_2 = .004; even 3-month BCR-ABL^{IS} ≤1%: 60.0% vs 21.2%, P <.001).

In combination with the above-mentioned findings that EMR achievement is a priority for MR4.0 achievement, we speculate that nilotinib is a better choice than imatinib for CML-CP patients who expect to achieve TFR. Moreover, this study indicated that the percentages of the patients who had a 6-month BCR-ABL^{IS} ≤0.1% did not differ significantly between those on nilotinib and imatinib therapy (40.7% vs 24.1%, P = .074), which is likely due to the small sample size for nilotinib therapy (only 33 cases). Further investigation is required with the inclusion of more CML-CP patients receiving nilotinib.

Taken together, our findings indicate that achieving MR4.0 should be a priority in CML-CP patients who have a 3-month BCR-ABL^{IS} ≤1% and 6-month BCR-ABL^{IS} ≤0.1%, which prompts us to reconsider the definition of an EMR when the main objective is DMR, or furthermore TFR. Moreover, nilotinib

seems to have a higher therapeutic value for CML-CP than imatinib, at least during the early stage of treatment.

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Software: Yue Cong.
Writing – original draft: Rui Wang.
Writing – review & editing: Hai Lin.

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