

Access this article online

Quick Response Code:



Website:  
[www.ijhonline.org](http://www.ijhonline.org)

DOI:  
10.4103/ijh.ijh\_2\_18

# Treatment outcome of 100 chronic myeloid leukemia patients using nilotinib as the 2<sup>nd</sup> line therapy

Yaseen M. Taher, Ali M. Almothaffar<sup>1</sup>, Bassam Francis Matti<sup>2</sup>, Alaa Fadhil Alwan<sup>3</sup>

## Abstract:

**BACKGROUND:** Nilotinib is a potent and selective BCR-ABL inhibitor approved for use in patients with newly diagnosed chronic myeloid leukemia (CML) in chronic phase (CML-CP) and in patients with CML-CP and accelerated phase (CML-AP) who are resistant to or intolerant of imatinib. Patients with imatinib-resistant CML, nilotinib treatment resulted in a significant proportion of patients achieving hematologic and cytogenetic responses in all phases of CML.

**OBJECTIVES:** The aim of the present study was to assess the treatment outcomes in term of the molecular response rate of CML patients using Nilotinib as the second-line therapy after failure of imatinib therapy.

**PATIENTS AND METHODS:** A prospective study conducted between December 2014 and December 2016 in Baghdad Teaching Hospital and National Centre of hematology. A total of 100 patients, who were on nilotinib therapy as the second-line therapy, were enrolled in this study. The molecular response was assessed using real-time quantitative polymerase chain reaction (RQ-PCR). Major molecular response (MMR) was defined as the BCR-ABL1 of <0.1% by RQ-PCR.

**RESULTS:** The median age was 39 years, 59 were female and 41 were male. Fifty-three patients were classified as high-risk group, and 47 patients were as low risk. The BCR-ABL transcription level had a significant reduction from baseline at 3 months ( $P = 0.035$ ) and the reduction from 3 months to 6 months was also statistically significant ( $P < 0.001$ ). Comparing the patients who achieved MMR versus NO MMR, there was a significant association between low European Treatment and Outcome Study score and achieving MMR. An estimated 24 months overall survival (OS) is 95%.

**CONCLUSION:** This study concluded that nilotinib is an effective therapeutic option for patients with CML-CP-resistant to imatinib therapy. Nilotinib treatment resulted in a high-OS rate and was well tolerated.

## Keywords:

Chronic myeloid leukemia, nilotinib, outcome

## Introduction

Chronic myeloid leukemia (CML) is one of myeloproliferative neoplasms which characterized by rearrangement of the long arms of chromosome 9 and 22, resulting in the Philadelphia (Ph) chromosome and driven by its product, BCR-ABL1 tyrosine kinase which is a result of fusion of BCR gene (on chromosome 22) and ABL1

gene (on chromosome 9) causing BCR-ABL1 fusion.<sup>[1,2]</sup>

The diagnostic criteria for CML according to the World Health Organization (WHO) require the detection of the Ph chromosome or its products, the BCR-ABL1 fusion mRNA and the BCR-ABL1 protein. This can be done by either conventional cytogenetic analysis (karyotyping), fluorescence *in situ* hybridization technique, or by reverse transcription polymerase chain reaction.<sup>[3]</sup>

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: [reprints@medknow.com](mailto:reprints@medknow.com)

**How to cite this article:** Taher YM, Almothaffar AM, Matti BF, Alwan AF. Treatment outcome of 100 chronic myeloid leukemia patients using nilotinib as the 2<sup>nd</sup> line therapy. *Iraqi J Hematol* 2018;7:67-71.

Department of Medicine,  
University of AL Iraqia/  
College of Medicine,  
<sup>1</sup>Department of Medicine,  
University of Baghdad/  
College of Medicine,  
<sup>2</sup>Department of Medicine,  
Hematology Unit, Baghdad  
Teaching Hospital,  
<sup>3</sup>The National Center of  
Hematology, Mustansiriyah  
University, Baghdad, Iraq

## Address for correspondence:

Dr. Yaseen M. Taher,  
Department of Medicine,  
College of Medicine,  
Al Iraqia University,  
Baghdad, Iraq.  
E-mail: [dr.yaseen1979@gmail.com](mailto:dr.yaseen1979@gmail.com)

Submission: 16-02-2018

Accepted: 21-04-2018

In 2011, the European Treatment and Outcome Study score (EUTOS score) was developed based only on the percentage of basophils in the blood and on spleen size and its predictive value was confirmed in a validation study of 2060 patients enrolled in studies of first-line treatment with imatinib-based regimens. In this study, EUTOS score was better than Sokal and Hasford score in predicting the probability of achieving complete cytogenetic response (CCyR) at 18 months and 5-year progression-free survival.<sup>[4,5]</sup> Monotherapy with a TKI that targets the ABL1 kinase is currently considered as standard treatment for CML-CP and AP.<sup>[6]</sup>

Imatinib mesylate has significantly improved the outcome of patients with CML in chronic-phase (CML-CP). In spite of the success of imatinib in treating patients with CML-CP, 34% of patients randomly assigned to the imatinib arm in resistance intervention after stroke trial was no longer on study drug at 6 years, for reasons that included lack of efficacy (12%) and the occurrence of adverse events (AE) (4%).<sup>[7]</sup> Resistance can emerge through several mechanisms, including point mutations in the BCR-ABL kinase domain.<sup>[8]</sup> For patients resistant or intolerant to imatinib, second-generation tyrosine kinase inhibitors which is more potent than imatinib. In addition to selectively inhibit BCR-ABL mutation, it also inhibits PDGFR and c-kit. It is also active against a range of imatinib-resistant kinase domain mutations, except for T315I, F359V/C, E255K/V, and Y253H/F.<sup>[9]</sup> Monitoring response to TKI therapy is one of the key management strategies of CML.<sup>[10]</sup> Response to TKI therapy is determined by the measurement of hematological, cytogenetic, and molecular responses. The goal of TKI therapy is to achieve a major molecular response (MMR) (define as BCR-ABL1 <0.1%) within 12 months of initiation of therapy to prevent disease progression to accelerated or blast phase according to ELN guidelines.<sup>[10]</sup>

The main objective of this study, open-label was to determine the efficacy of nilotinib in patients with Ph<sup>+</sup> CML patients in accelerated phase who are resistant or intolerant to imatinib therapy.

## Patients and Methods

### Study design and patient selection

This prospective cohort study conducted on 100 Iraqi CML patients, it was done in Baghdad Teaching Hospital and National Central of hematology in Baghdad, from December 2014 to December 2016.

Eligibility criteria for inclusion of patients were as follows: patients with CML-CP who were 18 years of age and more if they had imatinib resistance or intolerance, good performance status (the WHO

Performance Score 1), and normal hepatic, renal, and cardiac functions. Resistance was defined as no complete hematological response (CHR) at or after 3 months; no minimal cytogenetic response by 6 months; no major cytogenetic response (McyR) by 12 months; loss of CHR; loss of minor cytogenetic response; loss of MCyR or CCyR; or the development of clonal evolution. Imatinib intolerance was defined as discontinuation due to a Grade 3/4 imatinib-related AE. This study was conducted by the Declaration of Helsinki, and all patients gave their written informed consent according to institutional guidelines. The protocol was reviewed and approved by an Institutional Review Ethical Committee at each participating center. Patients are given nilotinib at a dose of 400 mg twice daily (800 mg/d) and they were followed for survival.

### Definitions of endpoints

The primary objective of the study was to determine the incidence of MMRs in patients resistant or intolerant to imatinib. This is the best cumulative response, with molecular assessments performed at 3, 6, and 12 months and then every 6 months in the 1<sup>st</sup> year and every 3–6 months in subsequent years.

The secondary objectives were to determine the overall survival (OS) which was calculated from the start of nilotinib to death due to any cause, as well as to determine the safety profile of nilotinib. Duration of response was defined as the time from the start of the response to the date of discontinuation due to progression or death. Calculation of the EUTOS score done by counting the basophil percentage in peripheral blood along with splenic size in cm as in following formula ( $7 \times \text{basophils} + 4 \times \text{spleen size}$ ); therefore, a score of more than 87 is considered to be high risk, while score  $\geq 87$  consider being low risk.

All time-to-event analyses were performed with the use of Kaplan–Meier methods and presented by Kaplan–Meier curves SPSS 20.0.0 (Chicago, IL) Minitab 17.1.0 software packages were used for statistical analysis and a  $P < 0.05$  was considered indicative of statistically significant difference.

## Results

The study group included 100 patients, mean age of patients at diagnosis was  $39.1 \pm 11.5$  years, and female-to-male ratio was 1.4:1. Forty-seven patients were considered as low-risk group according to the EUTOS score, and 53 patients as high-risk group. Median duration before receiving nilotinib was 42 months. Patients had either primary failure (17%) or loss of MMR (83%), they were offered nilotinib therapy 400 mg twice daily. At the end of follow-up, 5% of the patients

had died, of them, 3 had blast transformation, time to achieve MMR has a median of 9 months [Table 1].

The BCR-ABL transcription level had a significant reduction from baseline at 3 months ( $P = 0.035$ ) and the reduction from 3 months to 6 months was also statistically significant ( $P < 0.001$ ) as illustrated in Figure 1. Comparing the patients who achieved MMR versus No MMR, there was a significant association between low EUTOS score and achieving MMR [Table 2].

The estimated mean OS of CML patient since starting nilotinib using Kaplan Meier survival formula was 82.9 months; however, patients with low risk (using the EUTOS score) had better survival of 92.2 months, while those with high risk had shorter duration of survival of 58.3 months, despite this differences in survival it was not statistically significant (hazard ratio = 4.996, 95% confidence interval [CI]: 0.529–47.216).

Patients achieving MMR had significantly longer cumulative survival THAN those who did not achieve MMR (93.1 versus 56.5 months, respectively), the hazard ratio of 9.320 (95% CI: 1.037–83.738) [Table 3 and Figures 2 and 3].

All adverse effects hematological and nonhematological were either grade 1 or 2 as follows: Skin rash occurred in 14% of patients, joint pain 5%, palpitation 5%, anemia 4%, leukopenia 3%, headache 3%, thrombocytopenia 2%, hair loss 2%, Jaundice 2%, and 1% for each of the following: generalized edema, peripheral arterial obstruction, and peripheral neuropathy.

## Discussion

This study showed that nilotinib treatment was effective in CML patients after imatinib failure, in which 67% of the patients achieve MMR and an estimated 24 months OS of 95%.

The result of this study was higher when compared to that of Ayala *et al.*,<sup>[11]</sup> in which Nilotinib-induced CCyR was in 60%, and he found that molecular responses were 48% in the 110 patients treated, 58% of whom were MMRs, and 42% were deep molecular response.

In TIDEL-II trial,<sup>[12]</sup> CML patients were enrolled in two sequential cohorts in which they initially started on imatinib 600 mg/day then either escalated to 800 mg/day imatinib or nilotinib 800 mg/day, for the nilotinib cohort 87% and 83% of the patients achieved MMR after 12 and 24 months, 22% and 33% achieved MR4.5 after 12 and 24 months, respectively, compared to our findings TIDEL-II showed higher MMR.

**Table 1: Demographic and disease characteristics for chronic myeloid leukemia patients**

Variables	Values
Age (years) on diagnosis of CML, mean±SD (range)	39.1±11.5 (18.0-67.0)
Sex, n (%)	
Female	59 (59)
Male	41 (41)
EUTOS score on diagnosis of CML, n (%)	
Low risk	47 (47)
High risk	53 (53)
Cause of shifting to nilotinib, n (%)	
Primary failure	17 (17)
Secondary failure	83 (83)
Duration on nilotinib therapy (months)	10-95
Blast transformation during nilotinib treatment, n (%)	3 (3)
Death, n (%)	5 (5)
MMR, n (%)	67 (67.0)
No MMR, n (%)	33 (33.0)
Time to achieve MMR (months), median (IQR)	9 (4-13)

SD = Standard deviation, CML = Chronic myeloid leukemia, EUTOS = European Treatment and Outcome Study, MMR = Major molecular response, IQR = Interquartile range

**Table 2: Comparison between various variables according to achievement of major molecular response during treatment with nilotinib**

	MMR (67)	No MMR (33)	P
Age (years)	39.5±11.3	38.5±12.0	0.884
Sex (%)			
Female	39 (66.1)	20 (33.9)	0.819
Male	28 (68.3)	13 (31.7)	
EUTOS score (%)			
Low risk	41 (87.2)	6 (12.8)	<0.001
High risk	26 (43.4)	27 (56.9)	
Duration of disease before starting nilotinib (months)	44.8 (14.2-88.8)	33.5 (21.5-85.7)	0.817
Cause of shifting to nilotinib (%)			
Primary failure of imatinib	10 (58.8)	7 (41.2)	0.431
Loss of MMR after imatinib	57 (68.7)	26 (31.3)	

EUTOS = European Treatment and Outcome Study, MMR = Major molecular response

The results of this study differs from that reported by Kantarjian *et al.*,<sup>[13]</sup> in which MMR was achieved in 28% of the patients (294 patients had BCR-ABL transcript levels available during follow-up), they reported that patients at baseline with CHR had 38% MMR at the end while 22% had MMR in those without CHR, after 12 and 18 months 32% and 39% achieved MMR, respectively.

These variations in molecular response can be attributed to variations in designs and follow-up periods. Mean age

**Table 3: Overall survival of chronic myeloid leukemia patients since starting nilotinib measured using Kaplan–Meier method**

	Mean±SEM	95% CI of mean	HR	95% CI	P
Overall	82.9±7.1	69.1-96.8	-	-	-
EUTOS score					
Low risk	92.2±2.4	87.5-97.0	4.996	0.529-47.216	0.160
High risk	58.3±2.1	54.3-62.3			
Gender					
Female	58.5±2.0	54.6-62.3	4.203	0.431-40.940	0.216
Male	92.3±2.4	87.7-96.9			
Duration before receiving nilotinib (years)					
<2	22.2±0.6	21.1-23.3	0.013	0.46-43.737	0.035
≥2	86.4±7.2	72.3-100.5		P value 0.035	(S)
Cause of shifting					
Primary failure	58.1±4.6	49.1-67.1	2.940	0.487-17.752	0.240
Secondary failure	91.2±2.0	87.3-95.1			
Age at diagnosis (years)					
<40	91.2±2.4	86.5-96.0	1.284	0.207-7.970	0.789
≥40	73.0±6.3	60.8-85.3			
MMR					
MMR	93.1±1.6	89.9-96.3	9.320	1.037-83.758	0.046
No MMR	56.5±3.2	50.3-62.7			(S)

HR = Hazard ratio, CI = Confidence interval, SEM = Standard error of the mean, EUTOS = European Treatment and Outcome Study, MMR = Major molecular response, S = Significant

of our CML patients was 39.1 years which was similar to other Iraqi studies,<sup>[14,15]</sup> with median age 35 years, while it was younger compared to Kantarjian *et al.*<sup>[13]</sup> with a median age of 58 years, this variation in age are repeatedly observed, the median age of CML patients in Iraq is younger than what is seen in western countries<sup>[2,15]</sup>

The results of this study showed that the only significant predictor of MMR was the EUTOS score, in which low EUTOS associated with achieving MMR, this was similar to Larson *et al.*,<sup>[16]</sup> in which MMR rate was higher in lower risk group in both nilotinib and imatinib groups however that study utilized Sokal score but it satisfied the same conclusion reached by the EUTOS score. Switching from imatinib to nilotinib in <2 years, predicted lower cumulative survival after nilotinib therapy (22.2 ± 0.6 months) compared to 86.4 ± 7.2 months for those who had more than 2 years of imatinib therapy, indicating that rapid imatinib resistance leads to poor outcome even after conversion to the second-line therapy.

Achieving MMR is a significant predictor of longer OS in which patients achieving MMR had mean cumulative

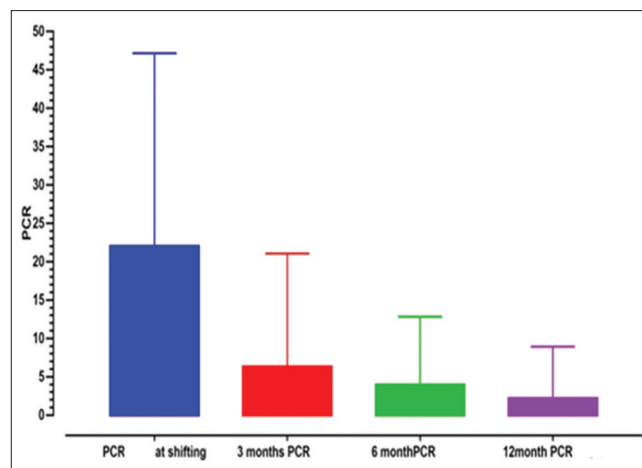


Figure 1: Change in BCR-ABL transcription level

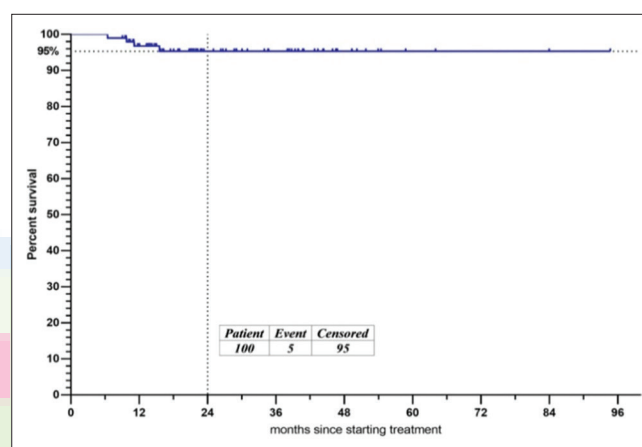


Figure 2: Overall survival of all patients

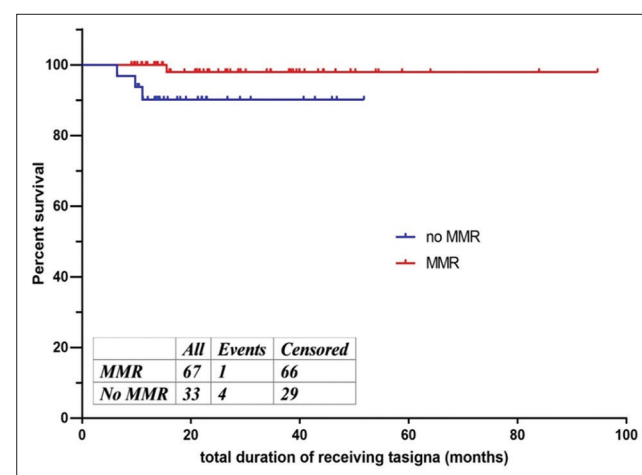


Figure 3: Overall survival according to achieving major molecular response

survival of 93.1 ± 1.6 months compared to 56.5 ± 3.2 for those without MMR, this result is similar to TIDEL-II trail.<sup>[12]</sup> Primary failure of imatinib lead to shorter OS (58.1 ± 4.6 months) compared to secondary loss of MMR (91.2 ± 2.0 months).



No significant hepatic, pancreatic, or cardiac events were observed during the follow-up period. A single peripheral arterial event was reported while no cerebrovascular or cardiac events occurred. The young age and low frequency of preexisting cardiovascular risk factors among patients in this study, as well as the limited follow-up duration for this analysis, may have contributed to the lack of observed cardiovascular safety issues in other studies.<sup>[17,18]</sup>

Consistent with prior studies,<sup>[19-21]</sup> this analysis showed the importance of the early molecular response to Nilotinib treatment. Patients with BCR-ABL1 10% at 3 months achieved the highest rates of response at later time points, whereas 10 out of 25 (40%) patient with BCR-ABL1 >10% at 3 months achieved MMR by 12 months compared with 57 out of 75 (76%) patients with BCR-ABL <10% at 3 month achieved MMR by 12 month. Five patients died in this study, 3 of them due to progression to documented blast crisis. The rate of blast phase was 2.1% (at 400 mg twice daily) in efficacy and safety in clinical trials-newly diagnosed patients (ENESTnd) study versus 3% in this study. The death rate from any cause was 3.5% (at 400 mg twice daily) in ENESTnd versus 5% in this study.

## Conclusion

This study confirms that nilotinib is an effective therapeutic option for patients with CML-CP resistant to imatinib therapy. Nilotinib treatment resulted in a high OS rate and was well tolerated.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

1. Rumpold H, Webersinke G. Molecular pathogenesis of Philadelphia-positive chronic myeloid leukemia – Is it all BCR-ABL? *Curr Cancer Drug Targets* 2011;11:3-19.
2. Alwan AF. Assessment of cytogenetic response after treatment with imatinib mesylate in patients with chronic phase chronic myeloid leukemia. *Iraqi J Hematol* 2014;3:56-61.
3. Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms. *Leukemia* 2008;22:14-22.
4. Marin D, Ibrahim AR, Goldman JM. European treatment and outcome study (EUTOS) score for chronic myeloid leukemia still requires more confirmation. *J Clin Oncol* 2011;29:3944-5.
5. Jabbour E, Cortes J, Nazha A, O'Brien S, Quintas-Cardama A, Pierce S, *et al.* EUTOS score is not predictive for survival and outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors: A single institution experience. *Blood* 2012;119:4524-6.
6. Saglio G, Hochhaus A, Hughes TP, Clark ER, Nakamae H, Kim DW, *et al.* ENESTnd update: Nilotinib vs. imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase and the impact of early molecular response and Sokal risk at diagnosis on long-term outcomes. *Blood* 2013;122:92.
7. Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L, *et al.* Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia* 2009;23:1054-61.
8. Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, *et al.* Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science* 2001;293:876-80.
9. Weisberg E, Manley P, Mestan J, Cowan-Jacob S, Ray A, Griffin JD, *et al.* AMN107 (nilotinib): A novel and selective inhibitor of BCR-ABL. *Br J Cancer* 2006;94:1765-9.
10. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF. Myeloproliferative neoplasms. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al.*, editors. *Lyon: WHO Press*; 2008. p. 31-65.
11. Ayala M, Domínguez J, Chavez A. Nilotinib as second or third-line therapy for myeloid chronic leukemia chronic-phase in Mexican patients. *Blood* 2016;128:5459.
12. Yeung DT, Osborn MP, White DL, Branford S, Braley J, Herschtal A, *et al.* TIDEL-II: First-line use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent molecular targets. *Blood* 2015;125:915-23.
13. Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, Gattermann N, *et al.* Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. *Blood* 2011;117:1141-5.
14. Almothaffar AM, Yassin BA, Murad NS, Alameri AM. Survival of patients with CML on imatinib experience with 44 Iraqi patients. *J Fac Med Baghdad* 2008;50:286-95.
15. Rahem RM, Alaawad AS, Kamoona TH. Evaluation of molecular monitoring and response milestone of patients with chronic myeloid leukemia to tyrosine kinase inhibitors in Middle Euphrates of Iraq. *Iraqi J Hematol* 2016;5:143-8.
16. Larson RA, Kim D, Issaragrisil S, le Coutre P, Dorlhiac Llacer PE, Etienne G, *et al.* Efficacy and safety of nilotinib (NIL) vs. imatinib (IM) in patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): Long-term follow-up (f/u) of ENESTnd. *Blood* 2014;124:4541.
17. Giles FJ, Mauro MJ, Hong F, Ortmann CE, McNeill C, Woodman RC, *et al.* Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: A retrospective cohort analysis. *Leukemia* 2013;27:1310-5.
18. Kim TD, Rea D, Schwarz M, Grille P, Nicolini FE, Rosti G, *et al.* Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia* 2013;27:1316-21.
19. Hanfstein B, Müller MC, Hehlmann R, Erben P, Lauseker M, Fabarius A, *et al.* Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia* 2012;26:2096-102.
20. Marin D, Ibrahim AR, Lucas C, Gerrard G, Wang L, Szydlo RM, *et al.* Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *J Clin Oncol* 2012;30:232-8.
21. Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boqué C, *et al.* Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood* 2014;123:494-500.