Higher Red Blood Cell Distribution Width Is an Adverse Prognostic Factor in Chronic-phase Chronic Myeloid Leukemia Patients Treated with Tyrosine Kinase Inhibitors

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Abstract. *The significance of red blood cell distribution width (RDW) was evaluated in patients with chronic myeloid leukemia (CML) in the chronic phase (CP). Eighty-four patients with newly-diagnosed CML-CP treated with any tyrosine kinase inhibitor (TKI) were analyzed. Patients were divided into two groups: a low-RDW group (RDW values ≤15%, n=31) and a high-RDW group (RDW values >15%, n=53). The 5-year event-free survival (EFS) and transformation-free survival (TFS) rates differed significantly between the low- and high-RDW groups (100% and 68%, respectively, in EFS, p=0.0071 and 100% and 81%, respectively, in TFS, p=0.039). The stratification by RDW had an impact on overall 5-year survival (100% in the low and 77% in the high RDW groups, p=0.047). We conclude that the RDW has a critical role in risk stratification of CML-CP patients for predicting treatment responses and outcomes.*

The introduction of the tyrosine kinase inhibitor (TKI) imatinib has dramatically improved outcomes for patients with chronic myeloid leukemia (CML) (1-3). At present, patients with chronic-phase CML (CML-CP) can attain long-term survival. Indeed, it has been shown that over of 80% of CML patients survive with imatinib treatment (1-3). Furthermore, the second-generation TKIs (2nd TKIs) nilotinib and dasatinib were approved as initial treatment agents for CML-CP based on the favorable results of two major randomized studies, ENESTnd and DASISION, testing the safety and efficacy of these TKIs compared to imatinib (4, 5). Although these treatment strategies appear promising, some patients still have an unfavorable prognosis when the treatment response is insufficient.

To date, treatment response as indicated by the cytogenetic or molecular evaluation at 3 months after initiating treatment is known as the most useful and reliable prognostic factor in CML-CP. Although scoring systems for CML-CP, such as Sokal, Hasford, and European Treatment and Outcome Study (EUTOS) scores, are also regarded as useful predictors of treatment, they often fail to predict patient outcomes including treatment response to TKI treatment (6-9).

We recently found that CML patients show anisocytosis at diagnosis, in most cases, that is improved after TKI treatment. The red blood cell (RBC) distribution width (RDW) is a simple parameter that can be obtained from the results of blood cell counts in clinical practice and reflects the distribution of RBC volume. Indeed, the RDW values in CML-CP patients were beyond the normal limit in most cases. In the present study, we report on the impact of RDW values on CML-CP patient outcomes and the role of RDW as a predictor of treatment responses based on the records of patients treated with TKI at our Institution.

Patients and Methods

Patients. We conducted a retrospective review of patient data from our Institution. Briefly, the study included patients who were more than 15 years old, diagnosed with CML-CP between April 2001 and January 2015, treated with any TKI as initial therapy, and followed-up for at least 3 months. CML-CP was diagnosed according to the European LeukemiaNet (ELN) criteria, described previously (10).

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Exclusion criteria were the use of interferon-α or any chemotherapeutic agent prior to or in combination with TKI treatment and mean corpuscular volume in RBC <80% at diagnosis. However, patients who received hydroxyurea prior to TKI treatment were included in the study. RDW values at diagnosis were obtained prior to treatment (including the use of hydroxyurea, TKI, or blood transfusion). The study was approved by the Research Ethics Boards of the Nihon University Itabashi Hospital and conducted in accordance with the Declaration of Helsinki.

Assessment of treatment response. Definitions of partial cytogenetic response (PCyR) and complete cytogenetic response (CCyR) were in accordance with the ELN 2013 recommendations (11). The disappearance of the Philadelphia (Ph) chromosome on G-banding analysis of the bone marrow, fluorescence *in situ* hybridization (FISH) analysis of the bone marrow, or FISH analysis of peripheral blood was regarded as CCyR. A major molecular response (MMR) was defined as less than the threshold of 0.1% of *BCR-ABL1/ABL1* transcript, according to the international scale (*BCR-ABL1^{IS}*) (10, 11). Detection of less than 100 copies of the *BCR-ABL1* transcript per microgram RNA by the transcription-mediated amplification and hybridization protection assay was also considered to be an MMR, as described previously (12-14). Response criteria to TKI treatment, including optimal, warning, and failure responses, were defined according to the ELN 2013 recommendations (10). Briefly, an optimal response was defined as achievement of PCyR or *BCR-ABL1^{IS}* ≤10% by 3 months, CCyR or *BCR-ABL1^{IS}* ≤1% by 6 months, and MMR by 12 months. A failure response was defined as an unattained complete hematological response or Ph >95% by 3 months, *BCR-ABL1^{IS}* >10% or unattained PCyR by 6 months, and *BCR-ABL1^{IS}* >1% or unattained CCyR by 12 months. Other responses were categorized as a warning response.

Statistical analysis. For all patients, overall survival (OS) was defined as the period from the date of initial treatment with TKI to the date of any cause of death or last follow-up. Event-free survival (EFS) was defined as the period from the date of initial treatment with TKI to the date of the first event or the last follow-up. Events were defined as two consecutive confirmations of loss of CCyR, progression to accelerated phase (AP), progression to blastic phase (BP), or any cause of death. Transformation-free survival (TFS) was defined as the period from the date of initial treatment to progression to AP or BP or the last follow-up. The Kaplan–Meier method was used to estimate EFS, TFS, OS, and cumulative CML-associated death. The log-rank test was used to compare EFS, TFS, OS, or CML-associated death between groups. Fisher's exact test, Mann-Whitney *U*-test, and two-tailed paired t-test were used to compare differences between the two groups appropriately. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for the R programming language (The R Foundation for Statistical Computing) (15).

Results

Patients' and treatment characteristics. There were a total of 90 newly-diagnosed CML-CP patients during the study period. Out of these 90 patients, 84 fulfilled the inclusion criteria and were analyzed. Among patients enrolled into the study, the RDW value ranged from 12.4 to 22.7%, and 62 of 84 (74%) showed higher than normal RDW values (normal range 11.4 to 14.4%). Patients were divided into two groups according to their RDW with the threshold value of 15.0%, which was determined to be the most predictive value for prognosis. The characteristics of these groups are presented in Table I. High RDW values were associated with female sex, higher WBC counts, higher probability of blast cells, lower hemoglobin levels, and splenomegaly. On the other hand, age, the probability of basophils or eosinophils, or platelet count was not associated with RDW values. With regard to scoring systems, risk stratification by the EUTOS score was associated with RDW values, while Sokal and Hasford scores were not. Furthermore, the initial treatment agent did not differ between the two groups.

Patient prognosis stratified by red blood cell distribution width. Next, the influence of RDW on patient prognosis was investigated. With a median follow-up period of 48 months (range=3-169), the 5-year EFS and TFS rates in the low- and high-RDW groups were 100% and 68%, respectively, for EFS and 100% and 81%, respectively, for TFS, which were significantly different (p=0.0071 for EFS; Figure 1A, p=0.039 for TFS; Figure 1B). Furthermore, the stratification by RDW had an impact on 5-year OS (100% in the low and 77% in the high RDW groups, p=0.047; Figure 1C). CML-associated deaths were only observed in the high-RDW group (0% in the low and 15% in the high RDW groups, for 5-year CML-associated death, p=0.050; Figure 1D).

The role of red blood cell distribution width as a predictor of treatment response. We investigated the extent to which RDW values could predict treatment responses, as measured according to the ELN 2013 recommendations. As shown in Table II, the high-RDW group was associated with significantly worse treatment responses by 3 and 6 months, while treatment responses by 12 months were not statistically significant.

Changes in red blood cell distribution width after tyrosine kinase inhibitor treatment. The changes in RDW values after TKI treatment were evaluated and the results are shown in Figure 2. The RDW values were transiently elevated at 1 month (median 15.8% at diagnosis and 16.4% at 1 month; p<0.001) and declined thereafter (median 15.6% at 3 months; p=0.971 compared to pretreatment). Furthermore, the RDW values were significantly lower 6 months after starting treatment compared to those at initial diagnosis (median 14.6% at 6 months; p<0.001).

Discussion

The results of the current study demonstrate the impact of the RDW on prognosis in patients with CML-CP who are treated with TKIs, including its associations with treatment response

Table I. *Patients' characteristics*.

	Low RDW (n=31)	High RDW (n=53)	*p*-Value
Age (years), median (range)	51 (23-83)	51 (22-85)	0.86
Gender female	5	25	0.0047
WBC counts ($\times 10^9$/L), median (range)	21.8 (9.2-702)	49.4 (7.9-468.2)	<0.001
Basophil (%), median (range)	6.5 (1.0-11.5)	6.0 (0-18.0)	0.919
Eosinophil (%), median (range)	2.5 (0-6.0)	2.5 (0.5-8.2)	0.0576
Blast (%), median (range)	0 (0-0.8)	0 (0-8.0)	<0.001
Hemoglobin (g/dL), median (range)	14.9 (10.1-18.8)	11.8 (5.8-15.6)	<0.001
Platelet counts ($\times 10^9$/L), median (range)	420 (205-2,110)	477 (118-1,792)	0.252
Spleen palpable	3	21	0.0052
Sokal score			
Low-risk	21	18	0.067
Intermediate-risk	7	21	
High-risk	3	14	
Hasford score			
Low-risk	12	17	0.421
Intermediate-risk	17	27	
High-risk	2	9	
EUTOS score			
Low-risk	30	35	<0.001
High-risk	1	18	
Treatment			
Imatinib	20	36	0.444
Dasatinib	7	13	
Nilotinib	4	4	

after 3 or 6 months. Recent reports have shown that treatment response at 3 months is predictive of outcomes in patients treated with TKIs, including imatinib, nilotinib, and dasatinib (16, 17). In agreement with the significance of early treatment response, the RDW value at-diagnosis was also predictive of outcomes, particularly by reflecting early treatment response at 3 months. In contrast to the majority of CML patients showing high levels of RDW, high platelet distribution width (PDW) was not as frequent, with only 18% of patients having higher PDW values. Furthermore, stratification by PDW value was not associated with patient prognosis.

Since our study results demonstrated the usefulness of the RDW as a prognostic factor, we speculated on reasons why RDW was predictive of treatment response and prognosis in patients with CML-CP. CML is a specific disease in which the CML stem cell has the potential to differentiate toward erythroid lineage cells, resulting in the involvement of malignant clone-derived erythropoiesis (18). Recently, it has been reported that somatic mutations in *IDH1/2*, *TET2*, or *ASXL1* are found in normal individuals along with those in advanced age and are associated with elevated risk of hematological disorders (19). Importantly, the study revealed that individuals harboring those mutations show significantly higher RDW values than those without it (19). Furthermore, it should be mentioned that these mutations are often present in CML cells and are associated with the disease status in CML patients (20, 21). Collectively, we hypothesized that the degree of dyserythropoiesis, indicated by a high RDW value, is possibly associated with the mutation status other than *BCR-ABL1* in CML clones, resulting in poor response to or resistance to TKI treatment. The correlations among RDW value, mutation status, and patient outcomes (including treatment response and prognosis) should be clarified. This notion remains to be investigated.

In our study, the EUTOS score was the only factor that was associated with risk stratification by RDW value. Because correlations between RDW value and Sokal or Hasford score were statistically insignificant, we investigated whether stratification by RDW value functioned as an independent factor. Our previous report showed that all the scoring systems had prognostic value for EFS and OS (22). When the influence of the Sokal or Hasford score and RDW values on EFS was evaluated by multivariate Cox proportional hazard regression model, the impact of those scoring systems disappeared and only RDW values remained as a prognostic factor. However, these results need to be verified in a larger sample size.

To date, baseline prognostic factors for the success of 2nd TKI treatment have not yet been determined while multiple predictors for the success of imatinib treatment have already been reported. Due to the high efficacy of 2nd TKI treatment, most prognostic factors associated with imatinib treatment

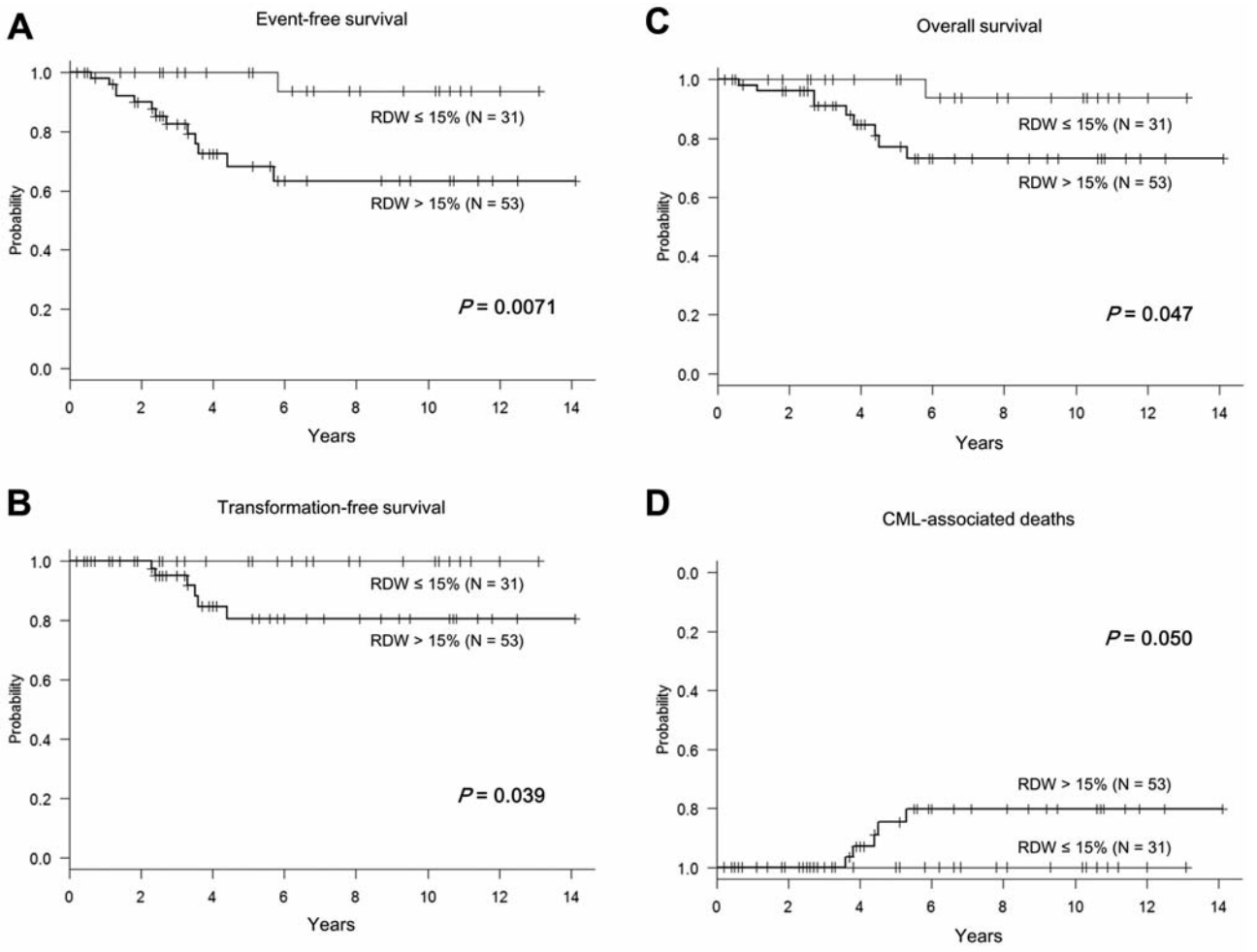

Figure 1. *Kaplan-Meier curves for event-free survival (A), transformation-free survival (B), overall survival (C), and chronic myeloid leukemia (CML)-associated deaths (D), according to red blood cell distribution width (RDW). Log-rank tests revealed significant differences between low and high RDW groups, with favorable outcomes in patients categorized into the low-RDW group.*

Table II. *Associations of red blood cell distribution width (RDW) and treatment responses according to European LeukemiaNet 2013 recommendations.*

	3 months optimal/warning/failure	6 months optimal/warning/failure	12 months optimal/warning/failure
Low-RDW (n=31)	22/1/0	23/3/0	16/3/3
High-RDW (n=53)	26/7/6	31/8/8	22/11/11
p-Value	0.0266	0.0396	0.254

seem to be overcome when other TKIs are used. Indeed, results of the D-First study published by the Kanto CML study group showed equivalent treatment responses to dasatinib between Sokal low and intermediate/high groups (23). Actually, there are no published data indicating the significance of scoring systems on prognosis in patients treated with 2nd TKIs. Therefore, the early treatment response is considered to be the only factor that predicts patient outcomes in those treated with 2nd TKIs. However, we assumed that the RDW value might become a new predictor of prognosis, even in patients treated with 2nd TKIs. This study included 28 patients treated with 2nd TKIs (20 dasatinib and 8 nilotinib). Among 2nd TKI-treated patients with available data, all 10 in the low-RDW group achieved optimal response at 3 months, while 3 out of

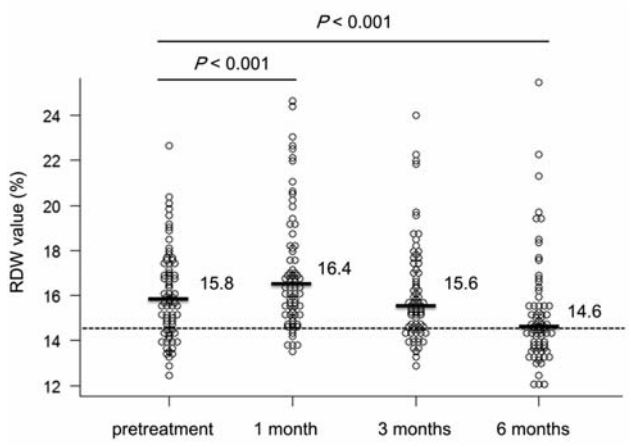

Figure 2. *Dynamics of red blood cell distribution width (RDW) before and after treatment with tyrosine kinase inhibitors (TKI). Seventy-two patients with available data encompassing 6 months of TKI treatment were subjected to analysis. The RDW values were transiently elevated at 1 month and declined thereafter. Furthermore, the RDW values were significantly lower 6 months after starting treatment compared to those at initial diagnosis. The black lines indicate the median value in each and the dotted line is the upper limit of the normal range for RDW values.*

13 did not in the high-RDW group. Although the number of cases is limited, the different probability of optimal response implies a possible role for risk stratification based on RDW in 2nd TKI-treated patients.

In conclusion, stratification of CML-CP patients according to their RDW value may predict treatment responses and such stratification could facilitate treatment planning. In the future, we hope to validate these findings in larger cohorts of patients with CML and separate patients based on the treatment agent. Investigations of the correlations between the RDW value, mutation status, and patient prognosis may provide new insights into CML therapy.

Conflicts of Interest

M.T. received research grants from Bristol and Novartis. N.I. received honoraria and lecture fees from Bristol and Novartis. Y.H. also received honoraria from Bristol and Novartis. The other authors declare no competing financial interests.

References

1 O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R and Druker BJ: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med *348*: 994-1004, 2003.

2 Kantarjian H, O'Brien S, Jabbour E, Shan J, Ravandi F, Kadia T, Faderl S, Garcia-Manero G, Borthakur G and Cortes J: Impact of treatment end point definitions on perceived differences in long-term outcome with tyrosine kinase inhibitor therapy in chronic myeloid leukemia. J Clin Oncol *29*: 3173-3178, 2011.

3 Tauchi T, Kizaki M, Okamoto S, Tanaka H, Tanimoto M, Inokuchi K, Murayama T, Saburi Y, Hino M, Tsudo M, Shimomura T, Isobe Y, Oshimi K, Dan K, Ohyashiki K and Ikeda Y: Seven-year follow-up of patients receiving imatinib for the treatment of newly diagnosed chronic myelogenous leukemia by the TARGET system. Leuk Res *35*: 585-590, 2011.

4 Saglio G, Kim D-W, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA and Kantarjian HM: Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med *362*: 2251-2259, 2010.

5 Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, Moiraghi B, Shen Z, Mayer J, Pasquini R, Nakamae H, Huguet F, Boqué C, Chuah C, Bleickardt E, Bradley-Garelik MB, Zhu C, Szatrowski T, Shapiro D and Baccarani M: Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med *362*: 2260-2270, 2010.

6 Yamamoto E, Fujisawa S, Hagihara M, Tanaka M, Fujimaki K, Kishimoto K, Hashimoto C, Itabashi M, Ishibashi D, Nakajima Y, Tachibana T, Kawasaki R, Kuwabara H, Koharazawa H, Yamazaki E, Tomita N, Sakai R, Fujita H, Kanamori H and Ishigatsubo Y: European Treatment and Outcome Study score does not predict imatinib treatment response and outcome in chronic myeloid leukemia patients. Cancer Sci *105*: 105-109, 2014.

7 Jabbour E, Cortes J, Nazha A, O'Brien S, Quintas-Cardama A, Pierce S, Garcia-Manero G and Kantarjian H: 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 *119*: 4524-4526, 2012.

8 Tiribelli M, Bonifacio M, Calistri E, Binotto G, Maino E, Marin L, Guardalben E, Branca A, Gherlinzoni F, Semenzato G, Sancetta R, Pizzolo G and Fanin R: EUTOS score predicts long-term outcome but not optimal response to imatinib in patients with chronic myeloid leukaemia. Leuk Res *37*: 1457-1460, 2013.

9 Bonifacio M, Binotto G, Calistri E, Maino E and Tiribelli M: EUTOS score predicts early optimal response to imatinib according to the revised 2013 ELN recommendations. Ann Hematol *93*: 163-164, 2014.

10 Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, Hjorth-Hansen H, Hughes TP, Kantarjian HM, Kim D-W, Larson R a, Lipton JH, Mahon F-X, Martinelli G, Mayer J, Müller MC, Niederwieser D, Pane F, Radich JP, Rousselot P, Saglio G, Saußele S, Schiffer C, Silver R, Simonsson B, Steegmann J-L, Goldman JM and Hehlmann R: European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood *122*: 872-884, 2013.

11 Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J and Hehlmann R: Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol *27*: 6041-6051, 2009.

12 Langabeer SE, Gale RE, Harvey RC, Cook RW, Mackinnon S and Linch DC: Transcription-mediated amplification and hybridisation protection assay to determine BCR-ABL transcript levels in patients with chronic myeloid leukaemia. Leukemia *16*: 393-399, 2002.

13 Yagasaki F, Niwa T, Abe A, Ishikawa M, Kato C, Ogura K, Sasaki H, Kyo T, Jinnai I, Bessyo M and Miyamura K: Correlation of quantification of major bcr-abl mRNA between TMA (transcription mediated amplification) method and real-time quantitative PCR. Rinsho ketsueki *50*: 481-487, 2009.

14 Ohnishi K, Nakaseko C, Takeuchi J, Fujisawa S, Nagai T, Yamazaki H, Tauchi T, Imai K, Mori N, Yagasaki F, Maeda Y, Usui N, Miyazaki Y, Miyamura K, Kiyoi H, Ohtake S and Naoe T: Long-term outcome following imatinib therapy for chronic myelogenous leukemia, with assessment of dosage and blood levels: The JALSG CML202 study. Cancer Sci *103*: 1071-1078, 2012.

15 Kanda Y: Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant *48*: 452-548, 2013.

16 Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boqué C, Chuah C, Pavlovsky C, Mayer J, Cortes J, Baccarani M, Kim D-W, Bradley-Garelik MB, Mohamed H, Wildgust M and Hochhaus A: Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). Blood *123*: 494-500, 2014.

17 Hughes TP, Saglio G, Kantarjian HM, Guilhot F, Niederwieser D, Rosti G, Nakaseko C, De Souza CA, Kalaycio ME, Meier S, Fan X, Menssen HD, Larson RA and Hochhaus A: Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. Blood *123*: 1353-1360, 2014.

18 Dainiak N, Liu A, Dewey MC and Kulkarni V: Chromosome analysis of isolated colony erythroblasts in chronic myelogenous leukaemia. Br J Haematol *56*: 507-512, 1984.

19 Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman P V, Mar BG, Lindsley RC, Mermel CH, Burtt N, Chavez A, Higgins JM, Moltchanov V, Kuo FC, Kluk MJ, Henderson B, Kinnunen L, Koistinen HA, Ladenvall C, Getz G, Correa A, Banahan BF, Gabriel S, Kathiresan S, Stringham HM, McCarthy MI, Boehnke M, Tuomilehto J, Haiman C, Groop L, Atzmon G, Wilson JG, Neuberg D, Altshuler D and Ebert BL: Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med *371*: 2488-2498, 2014.

20 Schmidt M, Rinke J, Schäfer V, Schnittger S, Kohlmann A, Obstfelder E, Kunert C, Ziermann J, Winkelmann N, Eigendorff E, Haferlach T, Haferlach C, Hochhaus A and Ernst T: Molecular-defined clonal evolution in patients with chronic myeloid leukemia independent of the BCR-ABL status. Leukemia *28*: 2292-2299, 2014.

21 Makishima H, Jankowska AM, McDevitt MA, O'Keefe C, Dujardin S, Cazzolli H, Przychodzen B, Prince C, Nicoll J, Siddaiah H, Shaik M, Szpurka H, Hsi E, Advani A, Paquette R and Maciejewski JP: CBL, CBLB, TET2, ASXL1, and IDH1/2 mutations and additional chromosomal aberrations constitute molecular events in chronic myelogenous leukemia. Blood *117*: e198-206, 2011.

22 Iriyama N, Hatta Y, Kobayashi S, Uchino Y, Miura K, Kurita D, Kodaira H, Inoue M and Takei M: The European Treatment and Outcome Study score is associated with clinical outcomes and treatment response following European LeukemiaNet 2013 recommendations in chronic-phase chronic myeloid leukemia. Int J Hematol *100*: 379-385, 2014.

23 Iriyama N, Fujisawa S, Yoshida C, Wakita H, Chiba S, Okamoto S, Kawakami K, Takezako N, Kumagai T, Inokuchi K, Ohyashiki K, Taguchi J, Yano S, Igarashi T, Kouzai Y, Morita S, Sakamoto J and Sakamaki H: Shorter halving time of BCR-ABL1 transcripts is a novel predictor for achievement of molecular responses in newly diagnosed chronic-phase chronic myeloid leukemia treated with dasatinib: Results of the D-first study of Kanto CML study group. Am J Hematol *90*: 282-287, 2015.

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