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Early BCR-ABL1 Reduction Is Predictive of Better Event-free Survival in Patients With Newly Diagnosed Chronic Myeloid Leukemia Treated With Any Tyrosine Kinase Inhibitor

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Abstract

The clinical prognostic factors during treatment are very important in chronic myeloid leukemia. An early molecular response and the halving time of BCR-ABL1 might be highly predictive of the outcome. A retrospective analysis of a cohort of 50 patients showed the importance of a very early molecular response in identifying subjects with favorable outcomes, using *ABL1* as the control gene for the analysis.

An early molecular response has a strong predictive value in chronic myeloid leukemia (CML). Recently, the halving time (velocity of early BCR-ABL1 transcript elimination) has been shown to represent an additional prognostic index. Our objective was the evaluation of the prognostic significance of the 3-month point in our population. We retrospectively collected BCR-ABL1 transcript data at different time points, events, and survival data of patients with CML treated at the Division of Hematology, San Luigi Hospital, University of Turin, Turin, Italy. Of 71 patients diagnosed from January 2005 to March 2015 in our center and treated with front-line tyrosine kinase inhibitors (imatinib, nilotinib and dasatinib), we selected those who had undergone a molecular evaluation at 3 months. The event-free survival (EFS) by the median follow-up time was the primary endpoint. The data from 50 patients with CML chronic phase were analyzed. Overall, 34 of the 50 patients (68%) had a transcript $\leq$ 10% at 3 months. Of those in the $>$ 10% group, 63% had experienced an event compared with 12% in the $\leq$ 10% group by the median follow-up point ($P < .001$). The halving time threshold for discriminating between EFS was 17 days. None of the patients with a transcript $>$ 10% at 3 months had a halving time of $\leq$ 17 days. Patients with BCR-ABL1 $\leq$ 10% and a halving time of $\leq$ 17 days had significantly better EFS than that of patients with BCR-ABL1 $\leq$ 10% and a halving time $>$ 17 days and of patients with BCR-ABL1 $>$ 10% (96% group 1 vs. 60% group 2 vs. 27% group 3; $P < .001$). Irrespective of the tyrosine kinase inhibitor used, the prognosis was significantly superior for patients with BCR-ABL1 $\leq$ 10% and halving time of $\leq$ 17 days. Our data revealed that the use of *ABL1* as a control gene is reliable for the determination of the halving time in the clinical setting and highlight the importance of measuring the BCR-ABL1 transcript at CML diagnosis.

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Introduction

Treatment of chronic myeloid leukemia (CML) aims at obtaining an optimal response, as defined by the international recommendations.[1]

Because more tyrosine kinase inhibitors (TKIs) are now available, much attention has been given to the identification of early prognostic markers during treatment. A strong predictive value has been observed for an early molecular response, with a BCR-ABL1 ratio $\leq$ 10% at 3 months and BCR-ABL1 ratio $\leq$ 1% at 6 months predictive of overall survival and event-free survival (EFS).[2-6] Early response landmarks could identify patients at greater

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risk of transformation who would benefit from an early switch to second-line therapy. It has also been demonstrated that the response at 3 months correlates with future major molecular responses (MMRs) and deep molecular response.[5,7,8] Although the prognostic significance of the BCR-ABL1 level at diagnosis remains controversial, it allows the assessment of early transcript kinetics (eg, between the diagnosis and 3 months of treatment).[8-10] Recently, the velocity of early BCR-ABL1 transcript elimination (ie, the halving time) has shown to represent an additional prognostic index.[10,11]

In a recent report by an Australian group, of 95 patients with BCR-ABL1 > 10% at 3 months, the patients with a BCR-ABL1 halving time of < 76 days had significantly superior outcomes compared with patients whose BCR-ABL1 values had not decreased by one half by 76 days.[11] Furthermore, the same investigators measured the prognostic significance of the rate of BCR-ABL1 decline at 1 month, demonstrating that of the high Sokal risk patients treated with imatinib, a halving time of ≤ 11 days was associated with outcomes equivalent to those of low Sokal risk patients.[12] Thus, we retrospectively analyzed our patients with CML to evaluate the prognostic significance of the 3-month point and to calculate the halving time thresholds for discriminating between EFS in our population.

Patients and Methods

A total of 71 patients were diagnosed with chronic phase CML in the Division of Hematology of San Luigi Hospital, University of Turin, Turin, Italy, from January 2005 to March 2015. These patients had been treated with front-line imatinib, nilotinib, or dasatinib (Table 1). For the present study, we included only those patients who had undergone molecular evaluation at 3 months. We analyzed the data retrospectively.

The patients were treated in accordance with the best standard of care. Since 2006, they were treated in accordance with the European LeukemiaNet (ELN) recommendations.[1,13,14] The patients were usually monitored by quantitative molecular evaluation every 3 months from the diagnosis.

ABL1 was used as the control gene. The level of BCR-ABL1 and total ABL1 were determined by quantitative reverse transcriptase polymerase chain reaction from peripheral blood samples using previously described standardized Europe Against Cancer protocols.[15,16] The final results were expressed as BCR-ABL1/ABL1 ratios in percentages according to the international scale, as previously recommended.[17,18] Molecular remissions were defined according to ELN criteria. MMR was defined as a 3-log reduction of BCR-ABL1 transcript levels, corresponding to ≤ 0.1% BCR-ABL1.[1] The MR4 and MR4.5 were defined according to the standardized definitions of the molecular response in CML.[19]

The main outcome measure was EFS by the median follow-up point. EFS was measured from the start of treatment to the date of any of the following events: treatment failure using the 2013 ELN recommendation definitions, progression to advanced phase, death from any cause, or reasons for changing treatment other than toxicity. EFS was estimated using the Kaplan-Meier method. The log-rank test was used to identify the significant differences between curves. Cox regression analysis was used to compute the hazard ratio to quantify the association between the early molecular response and deep molecular remission (MR4 and MR4.5). A receiver operating characteristic analysis was performed to calculate the optimal halving time threshold for discriminating between outcomes. The association between the halving time dichotomized at the threshold and the risk of an event was also evaluated.

Table 1 Patient Characteristics (n = 50)

Characteristic	n (%)
Median age at diagnosis (y)	59
Male gender (%)	72
Front-tine treatment	
Imatinib	33 (66)
Nilotinib	13 (26)
Dasatinib	4 (8)

The rate of BCR-ABL1 change from each patient's baseline value was assessed at 3 months of TKI therapy by estimating the number of days required for BCR-ABL1 to achieve one-half of the baseline value, termed the halving time. The halving time was calculated as reported by Branford et al,[11] in 2014 (ie, the ratio ln(2)/k, where k is the fold BCR-ABL1 change at the relevant point [3 months] from the baseline value divided by the number of days after the beginning of TKI therapy [day 0]).

Results

The data from 50 patients with chronic phase CML, with a median follow-up period of 61.8 months (interquartile range, 32.1-118.9 months), were analyzed. Of the 50 patients, 33 received front-line imatinib therapy, 10 received nilotinib, and 4 received dasatinib. Finally, 3 were enrolled in the Gruppo Italiano Malattie EMatologiche dell'Adulto CML0408 rotational protocol (NCT00769327) of nilotinib and imatinib (Table 1).

Of the 50 patients, 34 (68%) had a BCR-ABL1 transcript ≤ 10% at 3 months. At 6 months, 40 patients were evaluable for the treatment response. Of the 40 patients, 31 had a transcript < 1%. At 12 months, 48 patients were evaluable for the treatment response, and 20 had a transcript ≤ 0.1%. Of the patients who achieved a MMR at 12 months, 12 had been initially treated with second-generation TKIs. Only 5 of the 16 patients with a transcript > 10% at 3 months had a transcript < 1% at 6 months (Table 2). None of the patients with a transcript > 10% at 3 months had achieved an MMR at

Table 2 Responses and Events Stratified by BCR-ABL1 Transcripts at 3 Months

BCR-ABL1	BCR-ABL1 (%) > 10% at 3 mo (n = 16)	BCR-ABL1 (%) ≤ 10% at 3 mo (n = 34)	*P* Value
< 1% at 6 mo[a]	39 (5/13)	96 (26/27)	<.001
≤ 0.1% at 12 mo[a]	0 (0/16)	63 (20/32)	<.001
Total events	75 (12/16)	12 (4/34)	<.001

[a]Patients requiring a change of therapy before 6 months because of failure were considered evaluable but with no response (1 patient at 6 months, 4 patients at 12 months); patients requiring a change of therapy before 6 months because of intolerance were considered not evaluable (1 patient).