Adherence to Monitoring Tests in Patients With Chronic Myeloid Leukemia in Lebanon

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Abstract

The present study was performed to determine whether the adherence to regular follow-up assessments using standardized real-time quantitative polymerase chain reaction (qPCR) and/or cytogenetic tests in Lebanese patients with chronic myeloid leukemia (CML) meet the European LeukemiaNet recommendations. The present study was a retrospective analysis of 34 patients diagnosed with chronic phase CML who had been treated with tyrosine kinase inhibitors and monitored with regular cytogenetic tests and/or measurement of the BCR-ABL transcript level at 3, 6, and 12 months from 2006 until 2015 in 3 university hospitals in Lebanon. All patients were included and monitored in an adherence program (SAWA program). The male/female ratio was 3:1. The median age was 50 years, and the mean age was 50 years. As frontline treatment, 29 patients started imatinib and 5 patients received second-generation tyrosine kinase inhibitors. We defined compliance to the monitoring tests as regulary realizing the qPCR at 3, 6, and 12 months. Of the 36 patients, 15 underwent the recommended tests at 3, 6, and 12 months, representing a compliance rate of 41.6%; 28 of the 34 patients underwent the recommended tests only twice in the first follow-up year. Only 14 patients underwent qPCR at 3 months. We believe that despite the inclusion of our patients in an adherence program, the compliance rate is still low. We also believe that greater effort is required to improve the adherence to regular follow-up examinations.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. S1, S101-4
Keywords: CML, Compliance, Cytogenetic, Molecular tests, Monitoring

Introduction

During the past 15 years, the chronic oral administration of tyrosine kinase inhibitor (TKI) drugs that specifically target the tyrosine kinase activity of the oncogenic proteins encoded by BCR/ABL1 rapidly and dramatically modified the treatment of chronic myeloid leukemia (CML), leading to important changes in the management of the disease and revolutionizing the outcomes of patients with CML.[1,2] TKIs have become the standard therapy for chronic phase (CP), Philadelphia-positive CML.

To ensure the best outcome, patients and physicians should understand the proper use of the available TKIs and the critical importance of compliance to the treatment and regular monitoring tests. Inadequate surveillance of patient response to TKI can lead to the late detection of those with a poor response and failure to optimize treatment. This can result in CML disease progression to the accelerated phase (AP) or a blastic crisis (BC) and subsequent death.[3-5]

Although excessive monitoring can have economic costs, the use of monitoring tests will be of more importance in predicting progression-free survival and long-term survival. Therefore, careful and close cytogenetic and molecular monitoring of the treatment response will help detect the development of first-line therapy noncompliance, resistance, or progression to advanced-phase disease, implying the need to switch to salvage treatment.[3,5]

The European LeukemiaNet (ELN) proposed recommendations for the management of CML in 2006, 2009, and 2013. They emphasized the proper management of the available drugs and the importance of evaluating and monitoring the response and the interpretation of the molecular and cytogenetic test results.[3,5,6]

In clinical practice, monitoring a patient with CML might not be as regular and rigorous as it is in clinical trials. The purpose of our study was to determine whether the adherence to regular follow-up examinations using standardized real-time quantitative polymerase chain reaction (RT-Q-PCR) and/or cytogenetic tests in Lebanese patients with CML met the ELN recommendations for monitoring CML.

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Submitted: Mar 23, 2016; Accepted: Mar 23, 2016; Epub: Apr 4, 2016

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.03.007

Patients and Methods

In the present retrospective analysis, we included all patients diagnosed with CP-CML who had been treated from January 2000 until March 2015 in 3 major university hospitals in Lebanon (Notre Dame des Secours University Hospital, Hotel Dieu de France Hospital, and Saint George's Hospital). The diagnosis was confirmed by the presence of the Philadelphia chromosome on cytogenetic testing and/or BCR-ABL transcripts on molecular testing. All patients received either first-generation TKIs (imatinib) or second-generation TKIs (nilotinib or dasatinib). Data were collected by reviewing the medical records, including the physician notes and/or the laboratory test results. All patients were included and followed up in an adherence program. Of the 48 patients diagnosed with CML, 12 were excluded from the present study because either they had been diagnosed before the publication of the 2006 ELN recommendations or they had not completed the 1-year follow-up period after the diagnosis, leaving 36 patients for our analysis.

To properly evaluate the adequacy of the monitoring tests, all available data during the disease course were collected. The monitoring tests included the diagnostic confirmatory tests and follow-up cytogenetic tests. The latter were performed with chromosome binding analysis of bone marrow cell metaphases.[3,5,7-10] Molecular monitoring testing was performed using RT-Q-PCR.[8-11] The complete blood counts were measured and checked during the treatment course; however, these data were not included in our statistical analysis.

The compliance to the monitoring tests was deemed acceptable if cytogenetic testing had been performed at 3, 6, and 12 months of treatment, every 6 months until a complete cytogenetic response (CCyR) had been achieved, and every 12 months if regular molecular monitoring could not be assessed and in the case of a suboptimal response or treatment failure. Compliance to molecular testing was deemed acceptable if RT-Q-PCR of the BCR-ABL transcript level had been performed every 3 months until a major molecular response (MMR) had been achieved and confirmed at least every 6 months. These criteria were based on the 2006 and 2009 ELN CML recommendations.[2,3,6]

Table 1 Baseline Patient Characteristics (n = 36)

Characteristic	n (%)
Gender	
Male	26 (72)
Female	10 (28)
Median age (y)	50
Cytogenetic testing result	36 (100)
Typical	23 (64)
Atypical	13 (36)
Molecular testing PCR (BCR-ABL)	36 (100)
CML phase at diagnosis	
Chronic phase	34 (94)
Accelerated phase	1 (3)
Blastic phase	1 (3)
Treatment	
Imatinib (400 mg/d)	29 (80)
Nilotinib	6 (17)
Dasatinib	1 (3)

Abbreviations: CML = chronic myeloid leukemia; PCR = polymerase chain reaction.

Table 2 Rate of Molecular and Cytogenetic Testing During First Year of Follow-Up

Testing Interval (mo)	Molecular Testing (%)	Cytogenetic Testing (%)
3	41.6	27
6	69	38
12	75	44

The therapeutic response to TKIs in CML can be assessed using either molecular testing alone or cytogenetic testing alone, depending on the local laboratory facilities. However, both cytogenetic and molecular tests have been recommended until a CCyR and an MMR have been achieved. Subsequently, quantitative molecular tests from peripheral blood samples alone might be sufficient.[3,12,13] Compliance was considered complete if both tests had been used until a CCyR or an MMR had been achieved. The criteria established by the ELN group in 2009 were used for definition of the cytogenetic and molecular response and the progression to an AP or a BC. Missing data were considered to indicate noncompliance, because no traceability was available to confirm the adequacy of testing.

The patient characteristics are listed in Table 1. The male-to-female sex ratio was 3:1. The median age was 50 years, and the mean age was 47 years. All patients had undergone a cytogenetic workup at diagnosis. Of the patients, 62% had a typical karyotype and 38% an atypical karyotype. All the patients had undergone molecular testing using RT-Q-PCR at diagnosis. Of the 36 patients, 34 were diagnosed at the CP, 1 in the AP, and 1 in BC. As first-line treatment, 29 patients started imatinib and 7 received second-generation TKIs. All patients treated by second-generation TKIs had been diagnosed during or after 2011.

Results

In the first year of follow-up, 41.6%, 69%, and 75% of the patients had undergone molecular testing at 3, 6, and 12 months, respectively. In contrast, 27%, 38%, and 44% of the patients had undergone cytogenetic testing at 3, 6, and 12 months, respectively (Table 2). The rate of those who had undergone cytogenetic and molecular testing at 3, 6, and 12 months in accordance with the ELN CML recommendations was 19%, 25%, and 33%, respectively (Table 3).

Of the 36 patients, 6 experienced treatment failure at some point during the disease course (1 at 6 months, 2 at 18 months, and 2 at 2

Table 3 Rate of Complete Compliance to Monitoring Tests During First Year of Follow-Up

Testing Interval (mo)	Molecular and Cytogenetic Testing Compliance (%)
3	19
6	25
12	33