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Evaluation of molecular monitoring and response milestone of patients with chronic myeloid leukemia to tyrosine kinase inhibitors in Middle Euphrates of Iraq

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Abstract:

BACKGROUND: In the last decade, tremendous changes occurred in the treatment and follow-up of the patients with chronic myeloid leukemia (CML), with continuous update in the close molecular monitoring of treatment for the presence of minimal residual disease.

OBJECTIVES: The objective of this study was to evaluate the molecular monitoring of patients with CML on tyrosine kinase inhibitor (TKI) treatment and categorization of those patients according to the European Leukemia Net (ELN) guidelines.

MATERIALS AND METHODS: This observational cross-sectional study was conducted among all patients with CML registered in Oncology and Hematology Centers in Middle Euphrates of Iraq including 244 patients from April 2013 to April 2016. Eligible patients were 199 cases while 45 cases were excluded from the study. Venous blood in ethylenediaminetetraacetic acid was collected with each time of molecular monitoring to assess the level of messenger RNA of breakpoint cluster region-Abelson (BCR-ABL) by quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) (Cepheid, Gene Xpert Diagnostic System).

RESULTS: Most of the patients were in young adult age group with disease predominance more in females than males. Majority of the patients (72%) achieved optimal response after 12 months of treatment according to the ELN guidelines and 28% showed primary resistance to TKI. Some patients with optimal response (9%) will develop secondary resistance to treatment.

CONCLUSION: Most of our patients achieved major molecular response after 12 months of treatment with TKI according to the ELN guidelines that reflect proper management and regular follow-up of the patients by quantitative RT-PCR for the detection of BCR-ABL level.

Key words:

BCR-ABL, chronic myeloid leukemia, Iraq, molecular monitoring, tyrosine kinase inhibitors

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In less than the last 10 years, the prognosis of chronic myeloid leukemia has changed from that of a fatal disease to a disorder amenable simply to lifelong oral medication and compatible with a normal lifespan. This change has been made possible by a deep understanding of the molecular pathogenesis and a determination to develop targeted and selective drugs.[1] Chronic myeloid leukemia (CML) is a chronic myeloproliferative disorder that results from expression of the constitutive tyrosine kinase activity of the BCR-ABL oncoprotein. More than 95% of the patients with CML are associated with acquired cytogenetic abnormality known as the Philadelphia chromosome, resulting from a reciprocal translocation that fuses the ABL1 gene (Abelson) on chromosome 9 to the BCR gene (breakpoint cluster region) on chromosome 22. Variant rearrangements involving other chromosomes may also occur.[2]

CML is the most common type of the chronic myeloproliferative disorders and accounts for about 15%–20% of all cases of adult leukemias, but <5% of all childhood leukemias. CML incidence is strongly related to the age, with average age of a person with CML is around 60 years while uncommon in children and

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teens. Men are somewhat more likely to develop CML than women.[3]

In Iraq, the registered cases of all types of leukemia (including acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia, CML, and nonspecified leukemias) during 2011 ranked third after breast, bronchus, and lung cancers and formed 7.28% of the most common ten cancers by site according to the Iraqi Cancer Registry, with an incidence of 3.01/100,000 of the population.[4]

The resultant oncogene encodes a fusion protein (BCR-ABL) with constitutively upregulated tyrosine kinase activity and differential molecular weight isoforms of BCR-ABL, commonly of 210-kDa oncoprotein. Differences in intrinsic kinase activity and cell context may influence the type of leukemia that arises with each BCR-ABL isoform and the development of therapeutic agents to treat these BCR-ABL-driven malignancies.[5]

Based on its role in malignant transformation, BCR-ABL has served as a target for therapeutic intervention in CML. Imatinib and other tyrosine kinase inhibitors (TKIs) specifically target tyrosine kinase activity of the oncogenic protein encoded by BCR-ABL gene. TKI is highly effective in the treatment of CML. However, some patients fail to respond, suboptimally, or will relapse because of primary or acquired resistance or intolerance.[6]

The treatment of patients with Philadelphia chromosome-positive CML with imatinib mesylate has resulted in complete cytogenetic response (CCyR) rates of 65% to 85%, major molecular response (MMR) rates of 40%–70%, and complete molecular response (MR) rates of 10%–40%. As most patients achieve CCyRs with modern therapy, there is a need to develop more sensitive and accurate monitoring tools to measure residual disease.[7]

The presence of the Philadelphia chromosome abnormality, t (9;22)(q34;q11), can be detected by routine cytogenetics, or the Philadelphia-related molecular BCR-ABL abnormalities by fluorescent *in situ* hybridization, or by molecular studies reverse transcriptase-polymerase chain reaction RT-PCR.[8] RT-PCR amplifies the region around the splice junction between BCR and ABL. It is highly sensitive for the detection of minimal residual disease. PCR testing can either be qualitative (Q-PCR), providing information about the presence of the BCR-ABL transcript, or quantitative, assessing the amount of BCR-ABL message. Qualitative PCR is useful for diagnosing CML whereas quantitative PCR is ideal for monitoring residual disease. Quantitative RT-PCR quantifies the level of BCR-ABL messenger RNA in peripheral blood by comparing transcript levels to one of the several specific control genes. Sensitivity of such test reaches to 0.01%–0.001% (one CML cell in 100,000 normal cells).[9]

Molecular studies have several advantages including (1) good correlation between marrow and blood levels and (2) detection of very low levels of residual disease. Limitations include (1) a substantial incidence of false-negative tests (RNA degradation, low sensitivity of a given assay); (2) a coefficient of variability, which may be up to 0.5 log; and (3) poor reproducibility of results. Wide variations of transcript levels may be simply due to technical reasons rather than real changes in CML burden.[7]

The results for an individual patient, expressed as a ratio of BCR-ABL transcript copies to control gene copies, can be converted into an international standard using established conversion factors. International Scale (IS) is a means for standardizing and validating a patient's PCR test results. It refers to a reference range for reporting quantitative PCR results for BCR-ABL of patients with Philadelphia-positive leukemias. IS was developed as a result of the IRIS [International Randomized Study of Interferon and STI571] trial). It is important to standardize PCR laboratories so that physicians in different medical centers or offices can all "speak the same language" and "use the same tool to measure."[10]

To best determine an individual's response to therapy, an operational set of goals, defined within specific time periods, have been established for all patients.[11]

As more patients achieve CCyRs with imatinib and other TKIs, there is interest in obtaining better MRs. A MMR has been defined as a reduction in transcript levels (BCR-ABL/reference gene) of at least 3 logs compared with a standardized baseline obtained from patients with untreated newly diagnosed CML.[7] Unlike MMR, there are various definitions of deep MR, including MR 4.0 (BCR-ABL1 <0.01%), MR 4.5 (BCR-ABL1 <0.0032%), and MR 5.0 (BCR-ABL1 <0.001%).[12]

Primary resistance to TKI includes those with failure to reach complete hematologic response, CCyR, and MMR, within an allocated duration of time,[13] while loss of a previously obtained response to treatment with TKI resulting in secondary or acquired resistance.[14]

The European Leukemia Net (ELN) definition of the response to TKIs at 6 and 12 months of treatment includes three response criteria as follows; optimal response at 6 months when the BCR-ABL1 ≤1% or Ph + 0 (CCyR), warning response when the BCR-ABL1 1%–10% or Ph + 1%–35% (PCyR), and failure response when the BCR-ABL1 >10% or Ph+>35%. While at 12 months, optimal response is BCR-ABL 1 ≤0.1% (MMR), warning response is BCR-ABL1 0.1%–1%, and failure response is BCR-ABL1 >1% or Ph+ ≥1%.[15]

In this study, we try to evaluate the molecular monitoring of patients with CML on TKI treatment and categorization of those patients according to the ELN guidelines.

Materials and Methods

Patients

Data of 244 patients with CML registered in three Oncology and Hematology Centers in Babylon, Najaf, and Karbalaa incorporation with Al-Nahrain Medical Laboratory included patient name, age, address, date of diagnosis, and serial records of molecular findings. Some additional information was completed for those without complete data available in their sheets by phone call or direct questionnaire.

Study design and setting

This is an observational cross-sectional study among a group of

Iraqi patients with CML registered in Oncology and Hematology Centers in Middle Euphrates of Iraq including Babylon, Najaf, and Karbalaa Centers living in the community of middle Euphrates of Iraq of different areas from Babylon, Najaf, Karbala, Diwania, Simawa, and Kut cities. This study was carried out from April 2013 to April 2016 to evaluate the molecular monitoring of patients with CML on TKI treatment and categorization of the patients on the map of international guideline.

This study was conducted in association with these three Oncology and Hematology centers and Al-Nahrain medical laboratory in Iraq-Karbala.

A total of 244 patients with CML were registered in these three Oncology and Hematology Centers, 45 patients were not eligible for the study either due to their new diagnosis (<3 months) or loss of their data or communication. The remaining 199 patients eligible for the study included those completed 6–12 months of treatment with TKI after diagnosis with available full data about their BCR-ABL level during the period of treatment [Figure 1].

Case definition and ascertainment

Inclusion criteria

All patients with CML registered in these three centers who complete 6–12 months of TKI treatment with available data of serial BCR-ABL level during the treatment were included in the study. Primary resistance patients include those completed 6–12 months of treatment with TKI and their MR to treatment was either warning (BCR-ABL level 1%–10% IS after 6 months or 0.1%–1% IS after 12 months) or failure (BCR-ABL level >10% IS after 6 months or >1% IS after 12 months) according to the ELN guideline for molecular monitoring of patients with CML on TKI.

Secondary resistance patients include those completed 6–12 months of treatment with TKI and their MR to treatment was optimal (BCR-ABL level <1% IS after 6 months or <0.1% IS after 12 months) according to ELN guideline but lose their response at any time during the period of treatment that did not fit for optimal response criteria.

Exclusion criteria

We excluded 45 patients with CML those registered in the Oncology and Hematology centers but either newly diagnosed (<3 months of treatment) or lost their data, lost communication, and poor adherence to treatment.

Adherence of patients to treatment was approved as possible with oral or phone communication with each patient to exclude the possibility of poor compliance as a cause of response failure.

- Permission from patients: The study protocol was conducted after obtaining permission from all centers included; in addition, verbal consent to the laboratory studies was obtained from each adult or child's parent participating in this study
- Assessment of exposure: After assessment of patients with CML who were eligible for the study, the molecular milestones of each patient were assessed and categorized according to the ELN guideline
- Potential confounders: Compliance of patients to the treatment was assessed to eliminate its effect on the results. Patients' adherence to treatment was prospectively investigated using a survey questionnaire but not with techniques of the Medication Event Monitoring System, calculation of the medication possession ratio
- Validation of the results: It was not done depending on the fact that Gene Xpert kit calibrated to the WHO international genetic panel for quantitation of BCR-ABL mRNA, with our limitation in the cost, time, and technical facility
- Power calculation: Cross-sectional study included all patients registered in these centers with no effect of the number on the power of study.

Materials and methods

Sampling

During the regular follow-up of the patients with CML, venous blood was taken from all patients in sterile venipuncture to assess the BCR-ABL oncogene level according to the national guideline for molecular monitoring depending on the ELN guideline. Two milliliters was collected in ethylenediaminetetraacetic acid (EDTA) tube for complete blood count (CBC) and measurement of BCR-ABL oncogene level by RT-PCR.

Complete blood count

CBC (including Hb, packed cell volume, red blood cell indices, white blood cell, total and differential count, and platelet count) was measured within 1 h of blood collection in EDTA tube using fully automated Hematology autoanalyzer (Swelab-Swede) in Al-Nahrain medical laboratory.

BCR-ABL level

The level of BCR-ABL messenger RNA p210 transcript in peripheral blood was measured using peripheral blood collected in EDTA tube that can be used immediately or can be stored for 2–3 days at 4°C. Quantitative RT-PCR (Cepheid Gene Xpert Diagnostic System, Cepheid, USA) that was standardized according to IS by comparing transcript levels to one of the specific control genes was calibrated to the WHO international genetic panel for quantitation of BCR-ABL mRNA, using Xpert BCR ABL monitor kit according to the manufacturer's recommendation, and the patients' result was expressed as % IS. This process was done in Al-Nahrain medical laboratory located in Karbalaa, Iraq, with license from the Iraqi Ministry of health (updating: no. 24625 on May 2, 2012).

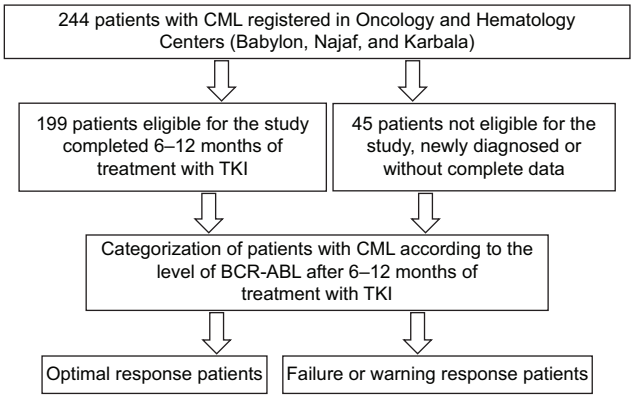

Figure 1: Flowchart of patients with chronic myeloid leukemia included in this study

Results

The demographic features of patients are illustrated in Table 1. Based on these data, mean age was calculated as 40.85 ± 15.09 for all patients, mainly in young adult age group with 6.55% of the patients are children <17 years of age. There was a difference between the number of male and female patients, as male-to-female ratio showing slight predominance in female patients (M:F; 0.82:1). It was noticed that the address of the patients was distributed in different areas of Middle Euphrates of Iraq including 84 cases from Babylon, 63 Najaf, 52 Karbala, 34 Diwania, 8 Simawa, 2 Kut, and 1 from Nasiriyah. The mean duration of all patients with CML was 46.05 ± 14.62 months.

About 72% of the patients achieved optimal response to TKI after 1 year of treatment while 28% did not, while after 6 months of treatment, 77% achieved optimal response compared to 23% who did not reach the recommended level of MR either in warning or failure group according to the ELN guideline for molecular monitoring [Tables 2 and 3].

After 1 year of treatment, 28% of the patients showed primary resistant to TKI and 9% of those with optimal response showed secondary resistance to treatment [Table 4].

Details of patients' result of their BCR-ABL level are shown in Table 5 that majority of the patients with optimal response (72%) after 12 months of treatment had oncogene level <0.1% IS (MMR, 3 log reduction) and others showed different levels of deep MR (4 log reduction and more).

Table 1: Demographic characteristics of patients with chronic myeloid leukemia (244 cases)

Characteristics	Findings
Age (years), %	
Mean (range)	40.85±15.09 (1-78)
0-10	2.7
11-20	8.3
21-30	14.8
31-40	19
41-50	26.9
51-60	19.5
>60	8.8
Adult CML (%)	228/244 (93.45)
Childhood CML (%)	16/244 (6.55)
Gender (male: female ratio)	112/136 (0.82:1)
Address	
Babylon	84/244
Najaf	63/244
Karbala	52/244
Diwania	34/244
Simawa	8/244
Kut	2/244
Nasiriyah	1/244
Duration of treatment (months), mean	46.05±14.62

CML = Chronic myeloid leukemia

Table 2: Categorization of patients with chronic myeloid leukemia at 12 months of treatment with tyrosine kinase inhibitor according to the European Leukemia Net guideline, 2013

Response according to ELN	Babylon center (%)	Najaf center (%)	Karbala center (%)	All patients (%)
Optimal response	74/96 (77)	36/58 (60)	34/45 (76)	144/199 (72)
Failure and warning response	22/96 (23)	22/58 (40)	11/45 (24)	55/199 (28)

ELN = European Leukemia Net

Table 3: Categorization of patients with chronic myeloid leukemia at 6 months of treatment with tyrosine kinase inhibitor according to the European Leukemia Net guideline, 2013

Response according to ELN	Babylon center (%)	Najaf center (%)	Karbala center (%)	All patients (%)
Optimal response	78/101 (77)	45/60 (75)	37/46 (80)	160/207 (77)
Failure and warning response	22/101 (23)	15/60 (25)	9/46 (20)	46/207 (23)

ELN = European Leukemia Net

Table 4: Distribution of resistance cases of patients with chronic myeloid leukemia

Resistance type	Babylon center	Najaf center	Karbala center	All patients (%)
Primary	22/96	22/58	11/45	55/199 (28)
Secondary	4/74	6/36	3/34	13/144 (9)

Discussion

In the last decade, tremendous changes occurred in the treatment and follow-up of the patients with CML, with continuous update in the close monitoring of treatment for the presence of minimal residual disease. The purpose of deep molecular response achieve by quantitative PCR for molecular monitoring for all CML patients on TKI will assess the response according to international guidelines of molecular monitoring like ELN and NCCN guideline.

Iraqi guideline for molecular monitoring depends on ELN guideline and mainly on the result of 12 month rather than 6 month of treatment to eliminate the bias of single reading of quantitative PCR , yet the optimum regular monitoring is at 6 month in Iraqi guideline. Demographic features of our patients show that most of the patients are in the young adult age group that was not similar to most of the concept of patients with CML worldwide, as in the UK, about half of the patients are diagnosed at 65 years and above with median age around 60–65 years at diagnosis.[16,17] CML is mainly a disease of adults, having increasing diagnosis with advancing age. Chronic leukemias are rare in childhood and represent 3% of pediatric leukemias, and childhood CML usually <5% of all cases like in the UK update registration represent 1.2% of all cases,[16,18] while CML in our patients shows an increased tendency to occur in childhood than the usual findings. These findings may be related to the biological molecular bases of the disease in our society or the nature of our patients that tend to develop the disease in younger age group. More deep research about the pathophysiology of the disease in our patients is required to determine the proper explanation of such findings. Similarly, CML in our patients occurred more in females than males and this also differs in most of the patients in another area of the

Table 5: Distribution of patients with chronic myeloid leukemia at 12 months of treatment with tyrosine kinase inhibitor according to the level of BCR-ABL level

BCR-ABL level (IS), %	Babylon center	Najaf center	Karbala center	Total	All patients
10-100	8	8	4	20	Failure and warning response
<10	5	6	4	15	(primary resistance) - 55/199 (28%)
<1	9	8	3	20	
<0.1	30	14	20	64	Optimal response - 144/199 (72%)
<0.01	16	8	2	26	
<0.0032	4	7	2	13	
<0.001	8	1	3	12	
No detection	16	6	7	29	
Total	96	58	45	199	

IS = International scale, BCR-ABL = breakpoint cluster region-Abelson

world[19] that shows male predominance than female, and again may be related to pathophysiology of the disease and why our females are more likely to develop CML than males.

Regular follow-up of our patients on TKI in the past few years will change the policy of treatment and put baseline for molecular monitoring similar to international guideline due to availability of treatment and presence of facilities to detect the BCR-ABL level by quantitative PCR and proper correlation between different oncology and hematology centers in our country.

Most of the patients in Middle Euphrates of Iraq are registered in Babylon Center because it is the oldest center in this area of our country and it has all requirements for this program similarly in the Najaf and Karbalaa Oncology and Hematology Centers.

At 12 months of treatment with TKI, 72% of our patients achieved MMR (BCR-ABL level <0.1% IS, log reduction 3) and this percentage reflects the proper treatment and follow-up of the patients in different centers according to the ELN guideline, while 28% of the patients showed warning and failure response to treatment at this time which may be related to resistance of patient, drug bioavailability, or even drug adherence of patients. Most authors show that more than 50% of patients on TKI treatment will optimally response after 12 months.[20] At 6 months of treatment, 77% of the patients showed optimal response, but at this point of treatment, the result may not reflect the real nature of the response and cannot depend on a single reading of oncogene level, so most of our assessment depends on 12-month treatment checkpoint for the residual disease. Primary resistance was seen in 28% of the patients on TKI while 9% of those with optimal response showed secondary resistance to treatment and increase in the level of BCR-ABL after initial well response. This secondary resistance may relate to common mutation or even new mutation effect on treatment activity.

BCR-ABL level in optimal response patients is at MMR (<0.1 IS) whereas the remaining at different levels of deep molecular response (< 0.0032 IS). Our monitoring was done with gene Xpert quantitative PCR that validated to detect deep MR to a level of 4 log reduction and even more deep but without certainty.

Conclusion

Most of our patients achieved MMR after 12 months of treatment with TKI according to the ELN guideline that reflects proper management and regular follow-up of the patients by quantitative RT-PCR for the detection of BCR-ABL level.

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Conflicts of interest
There are no conflicts of interest.

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