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ORIGINAL ARTICLE

# Response to tyrosine kinase inhibitors in chronic myeloid leukemia: experience from a west Asian developing country

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**Abstract** Tyrosine Kinase inhibitors (TKIs) have dramatically changed the prospects for patients with chronic myeloid leukemia (CML); however, information on CML and response to TKIs from Asia are limited, particularly from West Asia, including Iraq. To address the latter issue we evaluated and monitored a cohort of 108 Iraqi patients diagnosed as chronic phase-CML, enrolled in a government-sponsored national program. The patients were all treated initially by imatinib mesylate. Ninety-two percent of patients had a complete hematological response, 38 % had a major molecular response, while 79 % had a major cytogenetic response after a median follow-up of 35.7 months. The 3-year Event-Free, Progression-Free, and Overall survival rates were 79.6, 87 and 98.1 %, respectively. A total of 26 patients (24.1 %) were shifted to an alternative TKI (Nilotinib). After one year of therapy in seventeen of the latter patients, 24 % had major molecular response. In conclusion, our results compare favorably with those reported from the West and some Asian countries, and have demonstrated the importance of molecular as well as cytogenetic monitoring, and confirmed the relative success of the national CML program in our country.

**Keywords** Chronic myeloid leukemia · TKIs · Survival · Iraq

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## Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic disorder characterized by the malignant expansion of bone marrow stem cells. Its cytogenetic hallmark is a reciprocal t(9;22) (q34;q11) chromosomal translocation, which creates the derivative chromosome 22, Philadelphia chromosome (Ph). The latter harbors the BCR-ABL1 fusion gene encoding a chimeric protein with a deregulated tyrosine kinase activity, the expression of which has been shown to be necessary and sufficient for the transformed phenotype of CML cells [1].

The discovery of imatinib mesylate, a selective competitive inhibitor of BCR-ABL1 protein tyrosine kinase, was a major breakthrough in the management of CML since it induced both hematologic and cytogenetic remission in a significant proportion of patients [2]. Several scoring systems have been adapted to determine prognosis in patients on TKI [3, 4], and most recently the European leukemia net developed the European Treatment and Outcome Study (EUTOS) score using data from 2060 patients with newly diagnosed CML-Chronic phase treated with imatinib-based regimens. The EUTOS score was reported to have superior prognostic power compared with the previous scoring systems [5].

The success of the TKI imatinib mesylate, triggered further research into the development of other more potent

TKIs, and further generations were developed including Nilotinib, Dasatinib, Bosutinib and others. These TKIs were used initially for cases resistant to imatinib, and then their use was extended to first-line therapy [6]. Hematological, cytogenetic and recently molecular monitoring is necessary with the use of these agents, to evaluate response and consider alternative agents [7].

In some developing countries in Asia, one of the obstacles to favorable outcomes in CML is the prohibitive cost of TKI therapy and/or irregular availability of cytogenetic monitoring [8]. However, in Iraq, a country in west Asia, and for several years CML Iraqi patients were entered into a government-sponsored national program which ensures that they would have imatinib mesylate with regular cytogenetic monitoring. Therefore, the current study was initiated in order to assess the success of this program in a region in the north of the country, by evaluating a cohort of patients enrolled in this program and their response to TKI and the impact of introducing molecular monitoring on management decisions.

## Subjects and methods

In the period between September 2005 and December 2013, a total of 108 patients with Ph-positive CML (chronic phase according to WHO criteria) [9], from three major teaching hospitals in Iraqi Kurdistan were enrolled. All enrolled patients had peripheral blood cytogenetic FISH tests at diagnosis and follow-up, and all were treated with imatinib mesylate 400 mg/day orally. The molecular monitoring, on the other hand, was implemented regularly from August 2011 up to December 2013. All patients were hematologically and clinically evaluated at presentation and regularly thereafter. The EUTOS score was determined by the formula (7 × basophils) + (4 × spleen size). The spleen size was measured in centimeters below the costal margin and basophils as a percentage at baseline. A EUTOS score of more than 87 was considered as high risk, and less than or equal to 87 as low risk [5]. The study protocol was approved by the appropriate ethical committee. All patients gave written informed consent, according to institutional regulations.

### Response criteria

Complete hematological response (CHR) was defined as normalization of the peripheral leucocyte count $< 10 \times 10^9$/L (without peripheral blasts, promyelocytes and myelocytes) and platelets $< 450 \times 10^9$/L, in addition to the disappearance of all signs and symptoms of CML [10, 11].

Cytogenetic response was assessed using fluorescence in situ hybridization (FISH) analysis studies on peripheral blood. The latter was performed every 3 months until patients achieved a complete cytogenetic response (CCyR), and repeated annually thereafter. Cytogenetic response was defined as complete cytogenetic response (CCyR) if 0 % Ph-positive cells, partial cytogenetic response (PCyR) if 1–34 % Ph-positive, minor cytogenetic response (35–65 % Ph-positive cells), minimal cytogenetic response (66–95 % Ph-positive cells), and no response (>95% Ph-positive cells). Major cytogenetic response was the combination of both complete and partial cytogenetic responses [12]. The FISH analysis was performed at the laboratory of hematopathology and immunology in Baghdad-Iraq, using dual color-dual fusion kit from Applied Meta-system (Germany).

Molecular response expressed as log reduction in the BCR-ABL/ABL ratio, and achievement of 3 or more log reduction ≤0.1 % IS (international scale) in BCR-ABL/ABL ratio was called major molecular response (MMR) [13, 14]. The BCR-ABL major breakpoint cluster (BCR-ABL Mbcr) IS-MMR Kit (Ipsogen-FQPP-10-MMR-CE, France) was used for the accurate quantification of BCR-ABL transcripts following the manufacturer information.

The definitions of the survival end points as used in the current study (1) Event-Free Survival (EFS): defined as the time from treatment start until any of the following events while on treatment: (i) loss of complete hematologic response (CHR), (ii) loss of major cytogenetic response (MCyR), (iii) progression to Accelerated phase/blastic crisis, or (iv) death due to any cause.

(2) Overall survival (OS): is defined as the time from diagnosis to last follow-up.

(3) Progression-free survival (PFS): is defined as the time from treatment start until progression to accelerated or blastic phase during follow-up period [15].

### Criteria for changing to second generation TKI

1. Failure to achieve complete hematological response (CHR) at 3 months.
2. Failure to achieve any Cytogenetic response at 6 months (Ph + >95 %).
3. Failure to achieve major Cytogenetic response (MCyR) at 12 month.
4. Since August 2013, the criteria proposed by the European Leukemia Net for the management of chronic myeloid leukemia, including molecular criteria were adopted, as detailed elsewhere [14].

### Statistical methods

All statistical analysis was computed with SPSS statistical software (version 18). Statistical tests including Pearson Chi square test and Kaplan–Meier survival were used

**Table 1** Patient characteristics at diagnosis ($n = 108$)

| Parameter | Range | Median | Mean | ±SD |
|---|---|---|---|---|
| Age (years) | 7–83 | 44 | 45 | 15.1 |
| Hb (g/dl) | 4.8–16 | 10 | 10.2 | 2.0 |
| WBC $\times 10^9$/L | 13.5–640 | 106 | 135 | 111 |
| Platelet $\times(10^9$/L) | 100–987 | 296 | 339 | 190 |
| Blast (%) | 0–8 | 1.0 | 1.5 | 1.7 |
| Basophils (%) | 0–15 | 3.0 | 3.1 | 2.4 |
| Spleen size (cm, BCM) | 0–29 | 16 | 13.4 | 8.0 |
| Imatinib treatment duration (months) | 5–99 | 33.5 | 32.7 | 21.2 |

*BCM* below costal margin

whenever appropriate. A $p$ value $< 0.05$ was regarded statistically significant.

## Results

The mean age of the enrolled patients was 45 years (SD ± 15.1) and they included 57 (53 %) males and 51 (47 %) females with only one child aged seven years. The laboratory and clinical parameters that were observed at first presentation are shown in (Table 1).

### Response to therapy

All enrolled patients were initiated on imatinib mesylate at a dose of 400 mg/day, while the 7 years old child received imatinib at a dose of 200 mg/m$^2$ [16].

### Hematological response

Ninety-nine (92 %) of 108 patients achieved complete hematologic response (CHR) at the 3 months milestone, while the remaining 9 (8 %) patients did not achieve such a response, and were shifted to second generation TKI (Nilotinib) 400 mg orally twice daily.

### Cytogenetic response

After a median duration of treatment of 35.7 months (range 5–99 months) complete cytogenetic response (CCyR) was observed in 59 (55 %) cases, partial cytogenetic response PCyR in 26 (24 %), and minor, minimal, and no cytogenetic response (>35 % ph-positive) observed in 23 (21 %), as evaluated by peripheral blood FISH. The CCyR rates at (6, 12, and 18 months) after treatment were 47 of 108 (43.5 %), 59 of 108 (54.6 %), and 66 of 108 (61.1 %), respectively. The median time to CCyR was 7.1 months (95 % CI, 3.8–11.6). The cumulative incidence of CCyR was 62.9 % (68 of 108) (Fig. 1).

### Molecular response

Among the 100 patients who were >12 months at their last follow-up, 38 (38 %) had a major molecular response (MMR: <0.1 % IS), while 10 (10 %) cases had (0.1–1 % IS), and 19 (19 %) had 1–10 % IS, and the remaining 33 (33 %) had >10 % BCR-ABL IS.

### EUTOS scoring

Overall 63 (58.3 %) and 45 (41.7 %) of the 108 enrolled patients were assigned to the low and high EUTOS scores categories respectively [5]. The two EUTOS score categories and the related complete cytogenetic and major molecular responses were shown in (Table 2). The correlation between the CCyR, MMR and the risk score was statistically insignificant.

## Side effects of imatinib therapy

Three patients had grade (1/2) non-hematological side effects in the form of abdominal pain, myalgia, and joint pain, therefore they received the drug at a lower dose of 300 mg (instead of 400 mg) for 1–2 weeks, and later they resumed the full dose. All the latter three were in partial cytogenetic response, and around the 6 months treatment duration. Another three patients had stopped treatment on their own because they felt clinically stable and had complete hematological responses, and in all there were molecularly detectable RNA transcript levels. Therefore, they were re-instituted on the standard imatinib dosage. The rest of the patients have tolerated the treatment without significant side effects.

### Survival

Within the median follow-up period of 3 years, the event-free survival (EFS), progression-free survival (PFS), and the overall survival (OS) rates for the CML patients on TKI, were 79.6, 87 and 98.1 %, respectively (Fig. 2). Two patients died from blastic transformation to acute myeloid leukemia, one (48 months post diagnosis) died due to bleeding and the other (13 months post diagnosis) by multi-organ failure.

### Change of therapy

Out of 17 patients, 9 patients failed to achieve complete hematological response (CHR), and 8 patients were in CHR, but failed to achieve major cytogenetic response Ph >35 % at 1 year. Therefore, the treatment was changed to second generation tyrosine kinase inhibitor (Nilotinib

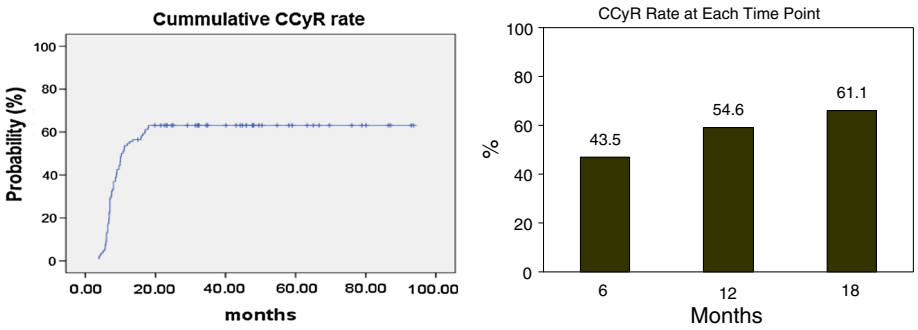


**Fig. 1** CCyR rates at 6, 12, and 18 months (actual response rates), and the cumulative response rate

**Table 2** EUTOS score categories and association with cytogenetic and molecular responses

| EUTOS risk score | CCyR number (%) (108 patients) | MMR number (%) (100 patients) |
|---|---|---|
| Low | 33 (52.3) | 20 (33.3) |
| High | 26 (57.7) | 18 (45) |
| *p* value | 0.579 | 0.24 |

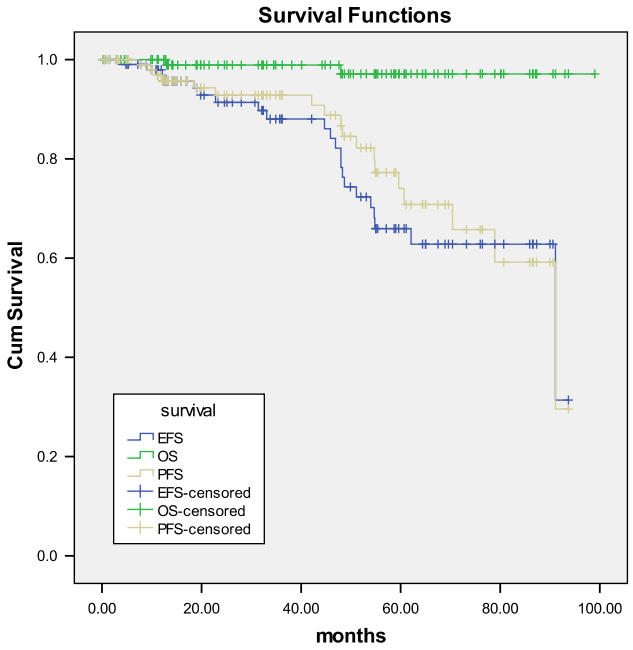


**Fig. 2** EFS, PFS, and OS of the 108 CML patients on treatment

400 mg twice daily). With the change of therapy, four patients experienced hematological toxicity (grade 3/4) and three patients had non-hematological toxicity (grade 3/4) for which the dose of the drug was modified for 1–2 weeks and resumed the full dosage thereafter. By 12 months, all the patients were in CHR, the CCyR achieved in 7 (41 %) cases, partial cytogenetic response in 6 (35 %) cases, while minor, minimal, and no cytogenetic response (Ph >35 %) showed in 4 (24 %) patients. On the other hand, the quantitative RT-PCR performed, 4 in 17 patients (24 %) achieved MMR (≤0.1 % IS). Three patients (18 %) are regarded in the warning category as they showed BCR-ABL transcript level (0.1–1 % IS), while 10 cases (58 %) failed to achieve the molecular response and have >1 % IS.

Molecular studies in patients who had complete cytogenetic responses after 12 months of therapy (56 patients) revealed that 18 (32.1 %) had a BCR/ABL detectable disease as documented by RT-PCR, including 9 patients whose BCR/ABL IS was >1 %. In the latter patients, imatinib was discontinued and the patients were put on Nilotinib 800 mg/day according to the new recommendation of ELN [14]; however, their outcomes are to be awaited.

## Discussion

The clinical and hematological characteristics of CML patients in the current study were to a great extent similar to those reported by western studies, except for the younger age and higher proportion of patients in the high EUTOS score category [17]. The younger age of our patients is consistent with that reported by earlier studies from Iraq, and studies from other Asian countries [8, 18, 19], while about 42 % of our patients were in the high risk EUTOS category compared to 10–11 % in Europe and USA and 30 % in Singapore [5, 20, 21]. Such a state makes evaluating response to TKI in our patients and its comparison to that reported by western studies justifiable, since such variables may have an impact on the response to such therapies.

The hematological response of 92 % to imatinib in the current study is expected, and rates ranging from 91.8–100 % have been reported in CML-CP from various studies throughout the world [2, 8, 15, 22]. Furthermore, our patients generally tolerated imatinib well at the 400 mg dose, similar to their Western counterparts and in contrast to some reports from Asian countries, e.g Hong Kong, where a majority of patients had low tolerance to the drug and could only tolerate doses of 300 mg or less [8].

**Table 3** Estimation of the EFS (event-free survival); PFS (progression-free survival); and overall survival in present and international studies

| Country, reference | Patients no. | Median study duration, years | OS % | PFS % | EFS % |
|---|---|---|---|---|---|
| IRIS Trial, Europe, O'Brien et al. [15] | 553 | 6 | 83 | 93 | 88 |
| USA (Jabbour et al. [20]) | 465 | 3 | 86 | 95 | 97 |
| DASISION Trial, USA, Saglio et al. [29] | 846 | 2 | – | 93.7 | 97.9 |
| PETHEMA group, Spain, Cervantes et al. [30] | 210 | 5 | 82.5 | 94.3 | 97.5 |
| China (Jiang et al. [31]) | 73 | 7 | 92 | 97 | – |
| Eastern India (Dasgupta et al. [35]) | 634 | 8 | 72.5 | 79 | 76.1 |
| CAMELIA International Registry, Czech and Slovakia Republics, Faber et al. [36] | 661 | 5 | – | 96 | 90 |
| Present study Iraq, 2013 | 108 | 3 | 79.6 | 87 | 98.1 |

Among the 108 CML-CP cases put on imatinib, major cytogenetic response (MCyR) was obtained in 79 % (which includes the complete and the partial cytogenetic response) after a median follow-up of 35.7 months. This result compares rather favorably with other studies from Europe and the USA, which reported major cytogenetic responses rates ranging from 60–90 % after median follow-up ranging from 18–60 months [2, 23–26], while one study from India reported a lower rate of 50.5 % after a median follow-up of 34.6 months [27]. Similar lower rates of 45–52 % were reported from other Asian countries like the Philippines [8].

It is interesting that our results compare well with the results of other studies despite the fact that our patients had higher EUTOS scores. Furthermore, there was no difference between the frequencies of CCyR in the two EUTO categories. This may be explained by the notion that the EUTOS score, like the Sokal score, measures the disease burden and may not reflect the dynamic of the disease in response to highly effective TKI therapy. The risk scoring systems in the TKI era may have lost some of its impact, since the most important individual prognostic factor today is the degree and timing of the hematologic, cytogenetic and molecular responses [28].

Molecular analyses have been set for the first time to our 108 CML patients and over the last 2 years. Our series has shown a MMR ($\geq$3 log reduction, $\leq$0.1 IS) in 38 % cases, and that was relatively comparable to the IRIS study, studies from USA and from Turkey at 38–40 % [15, 17, 22].

Our results showed EFS (79.6 %), PFS (87 %), and OS (98.1 %) which are to some extent similar to those reported by two American studies with comparable follow-up periods as shown in (Table 3) [20, 29], though EFS and PFS are lower, as would expected, when compared to other studies with longer median follow-up like PETHEMA study and the IRIS trial from Europe and Jiang and coworkers report from China where follow-up of 5,6 and 7 years, respectively [30, 31]. The high OS of (98.1 %) should be taken in the context of the shorter follow-up and the age of the enrolled patients, where most of our patients were in their 5th decade and thus with low rates of co-morbid conditions, and as documented by GIMEMA study group [23], age-related and not CML-related causes of death are responsible for mortality in older patients (Table 3).

Patients who achieve a CCyR in relation to the long term outcome; may be similar regardless of the time at which that is achieved, however patients who fail to attain a CCyR within the first 12 months of imatinib therapy have higher rates of disease progression and a lower probability of achieving an MMR [32]. The current study has revealed that around a third of those with CCyR had detectable BCR/ABL transcripts and in about half of the latter, it was in excess of 1 %, which would qualify them according to the ELN 2013 guidelines to be shifted to second generation TKIs, like nilotinib [14].

Nilotinib (AMN107), an oral novel second generation tyrosine kinase inhibitor is 20–50 folds more potent than imatinib. Nilotinib was used in patients who had CCyR but not MMR, as well for the 17 patients who failed to achieve CHR at 3 months, or experienced cytogenetic progression. For the latter 17 patients the analyses were repeated 12 months after nilotinib administration, and the results were acceptable (MMR in 24 %), compared to 28 % and 39 % by Kantarjian and coworkers [33], and Young Choi and coworkers [34], respectively. For the remaining cases who did not achieve the optimal responses, and based on the ELN 2013 guidelines, more careful and frequent molecular and cytogenetic tests within less than 3 months plus the mutational analysis are to be performed, and the patient should receive a alternative treatments whenever available and applicable, despite the fact that neither the mutational analyses nor treatments other than (Imatinib and Nilotinib) are manageable at our centers.

## Conclusion

This study showed that in a developing West Asian country, and despite the fact that CML patients were younger and were at a higher risk category, imatinib mesylate provided as a first-line therapy for chronic phase of chronic myeloid leukemia, was quite well tolerated and yielded results comparable to some extent to the western studies. The introduction of molecular in addition to cytogenetic monitoring had an important impact on treatment decisions, although it remains to be seen whether it would have an impact on overall survival. Finally, this study has also confirmed that nilotinib is an effective therapeutic option for many patients with chronic phase-CML resistant to imatinib therapy, and it was needed in about one quarter of the patients after a median of three years follow-up. However, the need for the provision of other alternative TKIs, as part of the national government-sponsored program, should be addressed in cases resistant to the latter drug.

**Conflict of interest** The authors declare no conflict of interest.

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