Effect of Imatinib therapy on liver enzymes and serum bilirubin in CML Iraqi patients

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Abstract:

Background: The treatment of chronic myeloid leukemia (CML) has been revolutionized by Imatinib. Imatinib is a selective inhibitor of the BCR-ABL tyrosinkinase, it produce high response rate in patients with CML who have no response to interferon alfa. Imatinib is occasionally associated with hepatotoxicity.

Objectives: The aim of this research is to study the effect of Imatinib therapy on liver enzymes and serum bilirubin in patients diagnosed in chronic phase myeloid leukemia.

Methods: A sample of 100 Iraqi patients diagnosed with CML, selected at random, at the National Hematology Center in Baghdad were included for the period from August till the end of October 2008. They were diagnosed by peripheral blood and bone marrow aspirate examination and real-time PCR. 98 patients were started on Imatinib mesylate 400 mg and only 2 patients were started on oral 300 mg daily. Liver enzymes and serum bilirubin were measured before starting treatment and after three months of continuing on treatment.

Results: Median age of patients was 35.5 years with 48 males and 52 females. The frequency of CML cases by residence was 46% from Baghdad and 54% from other regions of Iraq. The level of liver enzymes, serum alanine aminotransferase and serum aspartate aminotransferase was normal, serum alkaline phosphatase was normal in 94 patients, 5 patients had serum alkaline phosphatase less than 2 times elevated and one patient (18 years old) had 2 times elevates serum alkaline phosphatase level. The total serum bilirubin was normal in all patients.

Key words: Imatinib, Liver enzymes

Introduction:

Chronic myeloid leukemia (CML) is a clonal disease of the hemopoetic stem cell in which a reciprocal translocation, t(9;22) (q34;q11), forms the Philadelphia chromosome (Ph) and creates a novel fusion gene, BCR-ABL [1].

This gene expresses an activated tyrosine kinase that is central to the pathogenesis of CML [2, 3]. Imatinib mesylate is tyrosine kinase inhibitor that blocks the kinase activity of BCR-ABL, thus inhibiting the proliferation of Ph positive progenitors [4, 5]. Imatinib has shown activity against all phases of CML, though responses are most substantial and durable in patients who are in chronic phase [6, 7].

Most CML patients who receive Imatinib as first time therapy had achieved good cytogenic and molecular responses [7, 8].

Imatinib can cause a variety of non hematologic toxic effect; there may be abnormalities of liver enzymes that necessitate interrupting treatment [9]. A study of 44 Iraqi patients with CML who had been treated with Imatinib showed that only 2% had elevated serum transaminase [10]. Grade 2 or greater liver function test abnormalities are an indication to reduce the dose [11].

Patients & Methods:

The current study included a sample of 100 Iraqi patients in the chronic phase of CML (all were positive by using real-time PCR technique) who were selected at random. The diagnosis of CML was established by clinical presentation and laboratory data, peripheral blood and bone marrow biopsy examination. Clinical evaluation was done for all patients and investigations were performed for each patient including total serum bilirubin (Linear Chemical Company kit, Spain made), serum alanine aminotransferase (Biomeriex kit, France made), serum aspartate aminotransferase (Biomeriex kit, France made), and serum alkaline phosphatase (Biomeriex kit, France made).

The liver function tests had been done at the biochemistry laboratory of the National Center of Hematology in Baghdad at the beginning of the Imatinib course and after 3 months of the therapy.

It was difficult during the period of the study to do a proper follow up of patients because of the security instability that limits the sample size to only hundred patients and for such short period (3 months).

Descriptive statistics were done for the results as frequency, percentage, mean, standard deviation, minimum, and maximum value. The t-test for paired observations was applied to test the significance of difference of the means for different variables before and after 3 months of treatment with 0.05 as the level of significance.

Results:

One hundred Iraqi patients with CML with age ranging from 15 to 68 years; 80 patients were less than 50 years old (Figure 1) with a median age of 35.5 years; 48 were males and 52 were females (Figure 2); 46 were from Baghdad city and the rest were from other regions (Figure 3).

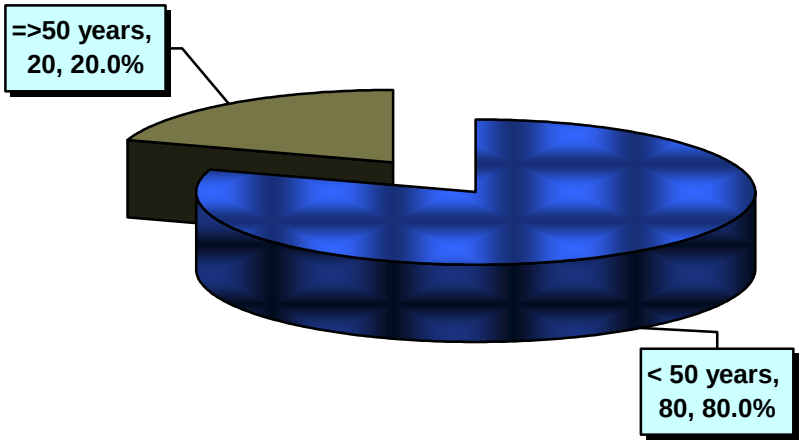

Figure 1: The age distribution of CML patients included in the study.

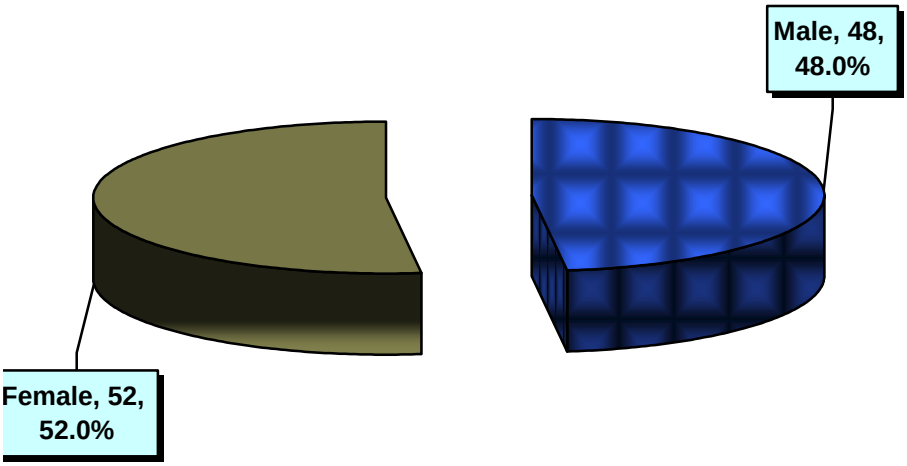

Figure 2: The sex distribution of CML patients included in the study.

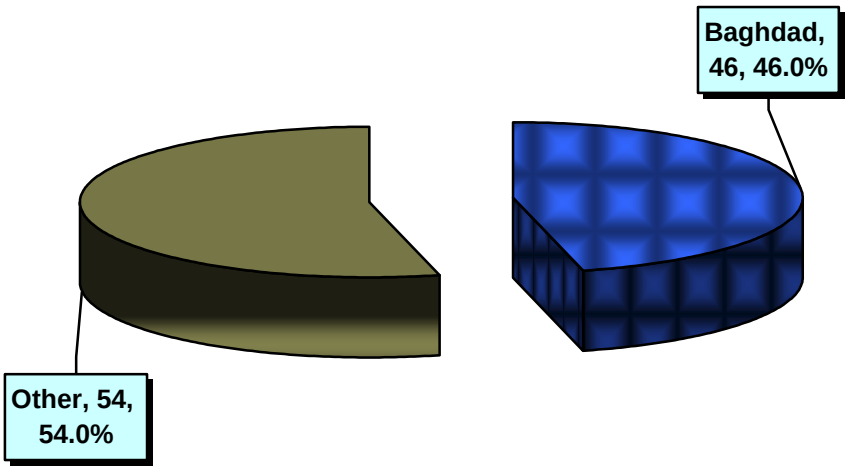

Figure3: The residence distribution of CML patients included in the study.

Table 1 shows the level of hemoglobin and platelet count before and after treatment with no significant difference while WBC shows a significant reduction as a marker for response to Imatinib.

Table 2 shows the laboratory results of total serum bilirubin, serum aspartate aminotransferase and serum alanine aminotransferase were no significant difference were found in these parameters before and after treatment. The level of these liver function tests were normal in all patients (100%), while serum alkaline phosphatase was normal in 94 patients (94%), one patient with more than two times elevation from normal level, and in the other 5 patients was less than two time elevation (Table 3).

Table 1: The hematological results {mean±SD (range)} of CML patients before & after 3 months of taking Imatinib.

	Before	After	P
Hemoglobin (g/dL)	10.30±1.55 (7.10-13.21)	11.20±1.45 (8.20-14.10)	>0.05
WBC ($x10^9$/L)	13.13±10.23 (3.19-85.96)	6.58±3.02 (2.90-10.60)	<0.05
Platelets ($x10^9$/L)	259.11±113.32 (58.00-533.00)	265.57±103.20 (59.00-554.00)	>0.05

Table 2: The liver function tests results {mean±SD (range)} of CML patients before & after 3 months of taking Imatinib.

	Before	After	P
Total serum bilirubin (mmol/L)	7.66±7.92 (2.00-18.00)	8.97±4.10 (3.00-20.00)	>0.05
Serum alanine aminotransferase (IU/L)	19.08±5.19 (8.00-23.00)	20.76±3.81 (10.00-29.00)	>0.05
Serum aspartate aminotransferase (IU/L)	22.55±6.63 (15.00-29.00)	24.44±4.36 (17.00-33.00)	>0.05
Serum alkaline phosphatase (IU/L)	55.35±29.89 (8.00-90.00)	60.72±32.56 (18.00-251.00)	>0.05

Table 3: The laboratory liver function tests results of CML patients after 3 months of taking Imatinib.

Liver function parameters	**No**	**%**
Total serum bilirubin Normal (3-21 mmol/L)	100	100
Elevated (>21 mmol/L)	-	-
Serum alanine aminotransferase Normal (<45 IU/L)	100	100
Elevated (≥45 IU/L)	-	-
Serum aspartate aminotransferase Normal (<40 IU/L)	100	100
Elevated (≥40 IU/L)	-	-
Serum alkaline phosphatase Normal (21-92 IU/L)	94	94
Elevated (>92 IU/L)	6	6

Discussion:

The results of the current study showed that the median age of CML patients was 35.5 years, which differs from Cortes *et. al* study in which the usual age was within the sixth and the seventh decade [12].

In order to determine the harmful effect of Imatinib therapy on liver enzymes of CML patients, total serum bilirubin, serum alanine aminotransferase, serum aspartate aminotransferase, and serum alkaline phosphatase were used while in other studies [10, 13] they used serum alanine and aspartate aminotransferase only.

These results showed that there was no increase in all theses enzymes except for the

elevated serum alkaline phosphatase which was found to be elevated in 6 patients (in one of them it reached about two times elevation) that can be represented as a side effect of imatinib, a result that is comparable to that of Jawad et al [10] of 2% transient elevation of serum transaminase.

These side effects were tolerable and did not necessitate discontinuation of Imatinib. In Hochhaus et al. study there was an increased serum alanine and aspartate transaminase levels [13] which was not similar to our finding. These differences from western studies may be due to differences in drug metabolism in different populations which can be genetically determined and is affected by alcohol consumption or use of other medications.

In conclusion, Imatinib for patient with CML is relatively non-hepatotoxic in this course duration (3months) that does not necessitate therapy discontinuation.

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