

## Imatinib Mesylate Effectiveness in Chronic Myeloid Leukemia patients in Upper Egypt

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**Abstract: Background and objectives:** Chronic myeloid leukemia (CML) is a relatively indolent hematologic malignancy that carries poor prognosis if left untreated; imatinib (IM) and other tyrosine kinase inhibitors (TKIs) have radically improved the outcome of patients with CML. The aim of the study was to evaluate the response of imatinibmesylate in CML and to observe the significance of Sokal score and various factors which predict the response. **Patients and methods:** A prospective study carried out in the department of clinical oncology of Assuit University Hospital; Twenty-three CML patients positive for bcr-abl were treated with Imatinib Mesylate from (May 2010 to May 2012), at the end of study Hematologic and cytogenetic response was analyzed according to various factors which predict the response and Sokalscore, the median follow-up of the patients was two years. **Results:** mean age was 49year range in age from (22-76) year. Among them 14 males and 9 females, treatment response were assessed in 19 patients, complete hematologic response CHR in (52%) of patients with a significant higher proportion of patients with chronic phase diseases CHR ( $P<0.01^*$ ). complete and partial cytogenetic response in (32% and 26% of patients respectively) and a significantly higher proportion of patients with chronic phase diseases and intermediate Sokel score achieved CyR ( $P<0.04^*$ ). **Conclusion:** Imatinibmesylate has substantial activity in CML, and a Lower Sokal score at time of presentation predict the higher cytogenetic response in patients with chronic phase CML.

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**Keywords:** chronic myeloid leukemia, chronic phase, imatinib, tyrosine kinase, sokal

### 1. Introduction:

Chronic myeloid leukemia is a chronic disorder of the bone marrow, characterized by the predominant unregulated proliferation of myeloid cells, and by the existence of a cytogenetic abnormality in the form of chromosomal translocation t (9; 22) (q34; q11) with BCR/ABL rearrangement.

Researchers directed their efforts at developing compounds that could selectively inhibit BCR-ABL tyrosine kinase which is abnormal enzyme, resulting in the development of a class of medications known as tyrosine kinase inhibitors (TKIs). Which are able to achieve long-term control of CML in the majority of patients; thus, they have become the initial treatment for almost all newly diagnosed patients with CML. All of the available TKIs (imatinib, dasatinib, and nilotinib) are able to induce hematological and cytogenetic responses in all stages of the disease (15-16).

Before the development of TKIs, allogeneic HCT remains the only treatment option with proven ability to cure CML especially for younger patients in chronic phase. However, as TKIs have demonstrated long term disease control and good tolerability, few patients choose allogeneic HCT as initial therapy. Instead, they are treated with TKIs and careful follow-up. Allogeneic HCT remains a principal therapeutic

option for patients who develop resistance or intolerance to TKIs.(20).

Imatinibmesylate, a selective BCR-ABL tyrosine kinase inhibitor is the first line therapy in patients with all phases of CML. It is proven to have significant benefits. Comparing imatinib versus interferon plus cytarabine for patients with newly diagnosed, chronic phase CML found that 97 % of patients who were given imatinib had a complete hematologic response rate, and 76 % achieved a complete cytogenetic response (15). Progression to blast crisis can occur despite imatinib treatment in patients with accelerated phase disease and in those who acquire new genetic mutations.

Despite the positive results obtained in previous studies, approximately 33% of patients with CML treated with imatinib do not achieve a complete cytogenetic response (CCyR), while others have drug resistance or cannot tolerate drug-related toxicities (3).

Prognostic scoring systems have been developed for risk stratification of patients with CML. Three prognostic systems are widely accepted in clinical practice: Sokal, Hasford and European Treatment Outcome Study (EUTOS). The Sokal score is based on patient age and clinical characteristics including spleen size, platelet count, and the percentage of blasts in the peripheral blood, and the Hasford model also includes eosinophil and basophil counts. Both systems

categorize patients as high, medium, or low risk, but the capacity of such measures to accurately predict response to treatment remains controversial. The EUTOS score is defined only by basophil count and spleen size. (7-18)

Swedish CML Registry recently reported that Sokal, but not EUTOS, predicted survival in a population-based cohort study. (19)

#### **Study design:**

This study was a prospective; phase II single institution study. The Ethics Committee in Faculty of Medicine, Assuit University, granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

## **2. Patients and Methods**

Our study was carried out at the department of clinical oncology of Assuit University Hospital; it involved Twenty-three CML patients from (May 2010 to May 2012), Before therapy, patient fulfill the inclusion criteria as follows:

All patients had morphologic evidence of CML and were positive for bcr-abl by reverse transcriptase-polymerase chain reaction (RT-PCR) and interphase fluorescence in situ hybridization (FISH).

Patients had an ECOG (Eastern Co-operative Oncology Group) performance status of 0–2.

Patients signed an informed consent form.

The exclusion criteria were as follows:

Ph chromosome negative CML patients were not included in the study.

Pregnant women or nursing mothers were not eligible.

Patients did not receive any other concurrent chemotherapy or radiation therapy during this study.

Patients with medical problems such as uncontrolled diabetes mellitus, hypertension, severe cardiovascular disease or active infections were not eligible for this study.

Imatinibmesylate was administered at a dose of 400mg/day in chronic phase and 600mg/day in accelerated phase, doses that were adjusted according to tolerance and response. Doses were reduced for neutropenia and thrombocytopenia grade 3 or 4.

Collection and analysis of epidemiological data (age, sex), clinical data (lymphadenopathy, splenomegaly, hepatomegaly, performance status, bone pain, and fever), biological data (white blood cell count, platelet count, hemoglobin count, blood blasts rates, blood promyelocytes biological data rates, and the result of cytogenetic or molecular biology), Sokal classification, treatment data (hematologic remission, cytogenetic remission and progression free survival).

#### **Definition of Treatment responses:**

Complete hematologic response (CHR) was defined as a total leukocytic count less than  $10 \times 10^9$

/l without immature granulocytes, with less than 5% basophils, and a platelet count less than  $450 \times 10^9$  /l. Complete cytogenetic remission corresponds to the absence of the Philadelphia chromosome at the cytogenetic examination (0% Ph + metaphases). It may be partial (1–35% Ph + metaphases) or minor (35%–95% Ph + metaphases) or minimal (96%–100% Ph + metaphases). Molecular responses were unavailable for most of our patients and thus were not included in analyses.

#### **Statistical methods:**

The frequency tables and standard descriptive statistics (mean, median, minimum, and maximum) were used to summarize patient characteristics.

Correlations of patients' data and therapeutic responses were assessed using Spearman's correlation test.

Level of statistical significance was set at 0.05. Analyses were performed using statistical software SPSS, 0.17.

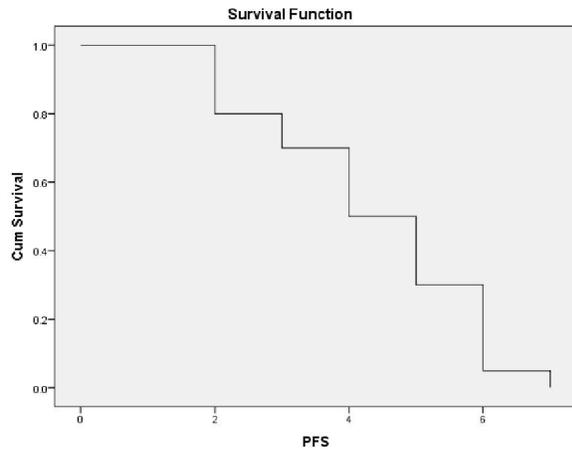
#### **Results:**

Twenty-three Philadelphia positive CML patients were treated with imatinibmesylate during the period (From May 2010 to May 2012). The epidemiological, clinical, and biological features of those patients are summarized in Table 1. Patients range in age from (22-76) year and mean age was 49 year. There were 14 males and 9 female, male: female ratio was 1.5:1, all patients were symptomatic with a Performance status was mainly 2 in (65%) of patients; splenomegaly in 100%, fever in 65% hepatomegaly in 35%, bone pain in 30% and lymphadenopathy in 13%, the median of white blood cell count was  $277 \times 10^9/L$ ;  $310 \times 10^9/L$ ; basophiles, blasts, and promyelocytes were respectively, 7, 3, 10 and the Sokal score was (65% of intermediate score and 35% of high score) 90% of the patients were in chronic phase while 10% in accelerated phase; treatment response were assessed in 19 patients where four patients were missed before start of treatment, (52%) of patients developed complete hematologic response (CHR) and (48%) of patients partial hematologic response (PHR). complete cytogenetic response in (32%) of patients, partial cytogenetic response (26%) of patients, minor cytogenetic response (26%) of patients, minimal cytogenetic response (16% of patients) (**Table 2**).

A significantly higher proportion of patients with chronic phase diseases, and intermediate sokel score achieved CyR ( $P < 0.04^*$ ) while a significant higher proportion of patients with chronic phase diseases achieved CHR ( $P < 0.01^*$ ). (**Table 3**).

The median PFS was 4 months (**figure 1**) and the only reported grade 3 or 4 was hematological toxicity. The outcome was fatal in 32%, and the causes of

death were dominated by hematologic toxicity in 50% of patients followed by infection in 33% of patients.



**Figure (1):** Progression free Survival Time in the study group.

**Table 1: Epidemiological, clinical, and biological features of patients.**

Variables	Numbers (%)
(22-76) 49	Age (years) mean age
<b>Sex:</b>	
Male-	(%61)14
-Female	(39)9
<b>Performance status: ECOG score</b>	
1	(%0)0
2	(%65)15
3	(35)8
4	(%0)0
<b>: Bone pain</b>	(%30)7
<b>Fever</b>	(%65)15
<b>Hepatomegaly</b>	(%35)8
<b>Lymphadenopathy</b>	(%13)3
<b>Splenomegaly:</b>	
10cm ≥	(%70)16
≥10cm	(%30)7
<b>Hemogram (median values and extremes)</b>	
-White Blood Cells:	277(99-396)
-Hemoglobin:	(11 - 6) 9
-Platelets:	310(1078-113)
-Blast cells:	3
-Basophiles:	(15 -2) 7
-Promyelocytes:	10 (4-18)
<b>Sokal score</b>	
-Low	0
-Intermediate	(%65)15
-High	(%35)8

**Table 2: Therapeutic features.**

Variables	Numbers (%)
<b>Phase:</b>	
Chronic phase	(%90)20
Accelerated phase	(%10)3
<b>Hematological remission:</b>	
Complete:	(%52)12
Partial:	(%48)11
Stable:	(%0)0
Progressive	(%0)0
-Major cytogenetic response (Ph+ ≤ 35%)	(%58)11(%32)6
Complete cytogenetic response (Ph+ 0%)	(%26)5
Partial cytogenetic response (Ph+ 1%-35%)	(%26)5
-Minor cytogenetic response (Ph+ 36%-95%)	(%16)3
-Minimal cytogenetic response (Ph+ 96%-100%)	
<b>Hematological toxicity: grade 3 and 4</b>	
:-Anemia	(%37)7
:-Leukopenia	(%26)5
:-Thrombocytopenia	(%32)6
<b>Outcome:</b>	
-Alive	13 (68%)
-Dead	6 (32%)
<b>Causes of death:</b>	
Hematologic toxicity	3 (50%)
Infection	2(33%)
Unspecified:	1(17%)

**Table 3: Correlations between patient characteristics and the hematologic and cytogenetic therapeutic responses**

Patients characteristic	Cytogenetic remission	Hematologic remission
	<i>p</i> -value	<i>p</i> -value
Phase:		
Chronic	<i>p</i> <0.04*	<i>p</i> <0.04*
-accelerated		
-Sokal Score:	<i>p</i> <0.04*	0.250 ns
-High		
-Intermediate		

**4. Discussion:**

The patients range in age from (22-76) years and The mean age of our patients was 49 years which was higher than that reported by other authors (5, 6) & significantly lower than the onset age observed in western countries (60-65 years) (2) and this could be attributed to smaller number of patients in our study and latter diagnosis. males were more affected than females (There were 14 males and 9 females, with

male: female ratio was 1.5:1) and this agree with Shereen *et al.* (17), This male predominance was also noted by Luatti *et al.*(13). Most of our patients were severely symptomatic with a performance status  $\geq 2$  in 100%, (splenomegaly in 100% which was relatively large,  $\geq 10$ cm in 30%), fever in 65%, hepatomegaly in 35%, bone pains in 30% and lymphadenopathy in 13%. whereas in the study by Koffi *et al.* (11) that were 59% of performance status was (0,1) and 10% had no splenomegaly ;however the long delays (consultation and treatment) contribute to alter the condition of the patient, to increase the volume of the spleen, white blood cell count and the Sokal score, and favor the transition to the accelerate phase of the disease. On the therapeutic level, we obtained complete hematologic response in 52% which was lower than those reported by Koffi *et al.* who had 76% of CHR while cytogenetic response was 32% in our study which was higher than those reported in the same study (11); the low rate of CHR could be related to the Sokal score (65% of intermediate score and 35% of high score with no reported low score) or to treatment interruption due to development of adverse events or drug unavailability due to financial issues. This explanation is supported by the work of others who demonstrated that treatment interruption leads to loss of the gained therapeutic responses and even to disease progression. (1-5).

In our study, there was MCR in 58%, CCR 32%, which are comparable with Jacob *et al.*, where MCR 55%, CCR 38%.(9).

As reported previously by Höglund *et al.* (8) we observed statistically significant differences in the PFS of CP-CML patients in the Sokal high-risk group and intermediate-risk group. PFS and CCyR were previously reported to be associated with the Sokal score, we have a significantly higher proportion of patients with chronic phase diseases, and intermediate Sokal score achieved CyR ( $P < 0.04^*$ ). The outcome was fatal in 32%, and the causes of death were dominated by hematologic toxicity (50%), followed by infection in 33%. Regarding the toxicities, generated by imatinibmesylate therapy, the significant difference has been observed in haematological toxicities. Incidences of neutropenia and thrombocytopenia are comparatively lower in other studies (9).

Patients, who are in disease progression or blast crisis, may acquire additional cytogenetic abnormalities. It may induce the conformational change of the BCR-ABL fusion protein further which may not be blocked by the tyrosine kinase inhibitor activities of imatinibmesylate alone. So, further molecular mutation detection are needed for these patients and accordingly new targeted therapy

(Nilotinib, Dasatinib, Basutinib etc.) (6) may be planned.

#### Conclusion:

**Imatinib mesylate has substantial activity in CML. Lower Sokal score at time of presentation predict the higher cytogenetic response in patients with chronic phase CML.**

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