Pattern of Hematological Response to Glivec in Chronic Myeloid Leukemia Patients

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Abstract:

Background: Chronic myeloid leukemia "CML" has emerged as a revolution in the success of our therapy. One can feel the triumph of medicine against cancer through the directed therapy that is now available for CML, making patients die with rather than from the disease. Now Imatinib Mesylate "Glivec" has changed the course of the disease. In this study we evaluate chronologically the hematological response of our CML patients in the era of this new drug that has been given the title of "the magic bullet against cancer".

Patient and Methods: Every patient seen and treated with Glivec was subjected to a critical evaluation in Kirkuk Hematology-Oncology Center. The standard dose for all patients is 400 mg orally daily. Following the pattern of response through CBC results available over the first 28 days of therapy were recorded first; for the rest of the first three months of treatment, weekly CBC was determined. Spleen size, Hb level and platelet count were also recorded. It is aimed to establish a platform for knowing how future patients with CML in our locality respond to Glivec treatment.

Results: The mean age of our patients was 44 years. Out of the 67 patients of CML, 35 were male and 32 were female. The first line treatment of all these CML patients was Glivec. We witnessed complete hematological response in (92.5%) of CML patients during the first three month after start treatment. Glivec has normalized the WBC count in the majority of our patients. Early neutropenia and thrombocytopenia necessitating manipulation of the standard Glivec daily dose of 400 mg.

Conclusion: Glivec is the target therapy in the management of the chronic myeloid leukemia with Philadelphia-positive chromosome and cause Complete hematological response that arise during the first three month after started treatment which lead to normalized WBC count and its differentiation in the blood smear with significant clinical improvement especially the size of spleen which become impalpable in (88%) of CML patients.

Keywords: Glivec, Chronic Myeloid Leukaemia, Hematological Response, Chronic

Introduction:

Chronic myelogenous or myeloid leukemia (CML), also known as chronic granulocytic leukemia (CGL), is a cancer of the white blood cells [(1)]. It is a form of leukemia characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood [(1)]. It is a type of myeloproliferative disease associated with a characteristic chromosomal translocation called the Philadelphia chromosome [(2)].

The Philadelphia chromosome was first recognized as a shortened chromosome 22, it was noted that the missing piece of chromosome 22 had in fact attached itself to chromosome 9, while a portion of chromosome 9 had translocated to chromosome 22[(3)].

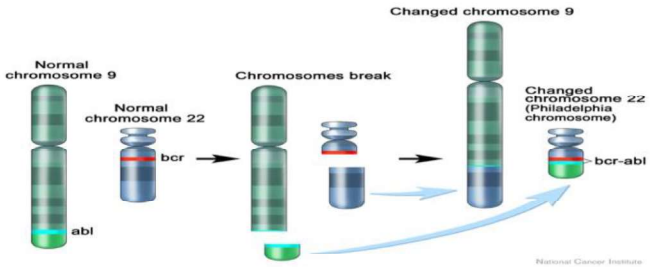

Figure (1): Philadelphia chromosome formation. Adapted from [3].

It is now treated with imatinib and other targeted therapies, which have dramatically improved survival. Chronic myeloid leukemia is characterized by a chronic (long duration) phase that is relatively benign. This disease, however, has a constant risk and tendency to transform into an acute blastoid (short duration) phase that is rapidly fatal [4].

Diagnosis:

CML is often suspected on the basis on the complete blood count, which shows increased granulocytes of all types, typically including mature myeloid cells. Basophils and eosinophils are almost universally increased. A bone marrow biopsy is often performed as part of the evaluation for CML, but bone marrow morphology alone is insufficient to diagnose CML [5].

Ultimately, CML is diagnosed by detecting the Philadelphia chromosome. This characteristic chromosomal abnormality can be detected by routine cytogenetics, by fluorescent in situ hybridization, or by PCR for the BCR-ABL fusion gene [6].

Classification: There are three phases of CML [7].

1. Chronic phase 2. Accelerated phase 3. Blast crisis.

Treatment of CML with Glivec:

Imatinib mesylate is now the standard and first line of treatment for CML. It is marketed as **Gleevec** or **Glivec** [8]. Imatinib is a small molecule kinase inhibitor. Gleevec film-coated tablets contain imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base [8].

Aims of the Study:

1. To prove that patients treated with Glivec has had significant increase in cure rate and overall survival.
2. Using the data to lay down the roadmap for future guidelines and course of action in dealing with treatment of chronic myeloid leukemia in the nation.

Patients and Methods:

This Study was performed over a 1year period in Kirkuk Hematology-Oncology Center. 67 patients diagnosed with Chronic Myeloid Leukemia "CML" were enrolled.

Patients were included in this study, provided that they met three inclusion criteria as the initial diagnosis:

(1) Persistent, unexplained leukocytosis.

(2) Presence of immature myeloid precursor (promyelocyte, myelocyte and metamyelocyte) in peripheral blood.

(3) Most important diagnostic parameters were Philadelphia chromosome and BCR/ABL transcript fusion gene is positive done.

(4) Hematological Data**:** Initial hemoglobin; platelet count; WBC and weekly do till first month then every two weeks during second month then the third month were evaluated for every patient.
(5) Sonographic findings**:** Regarding spleen size.

Results:

The total number of chronic myeloid leukemia patients in this study is 67 from this number (52%) of them are male and (48%) are female patients.
The age of the patients is between 14 to 82 years, the mean age is 44 years.
Initial hematological response including hemoglobin level; platelet count; WBC count and are weekly done during the first month then every two weeks during the second month then the third month were evaluated once for every patient.
Figure (2) shows the WBC counts responded well to Glivec during the first three months with a nearly normalized WBC count at the end of initial hematological response.
Figure (3) shows the hemoglobin level start to decrease at the first two weeks and then start to increase till it reaches the peak in the third month.
Figure (4) shows the minimal effect of Glivec to the platelet count especially at the end of the third month which shows the lowest mean of platelet count.
Regarding the splenic size, it has been divided into three categories and according to the ultrasonogarphic results. Normal spleen (long axis 10cm), mild to moderate splenomegaly (long axis 11-20cm) and huge splenomegaly (long axis >20cm) [13, 14, 15].
Figure (5) shows the percentage of huge splenomegaly in CML a patient at the time of diagnosis is about more than half of the cases. After three months of Glivec therapy the majority of patients showed returning of the splenic size to normal.
Figure (6) show (88%) of the CML patients normalized the spleen size while just (12%) of patients remained to have mild to moderate splenic enlargement.
Table (2) shows a highly significant response to Glivec in the changes of WBC count, Hb level and platelet count between the time of diagnosis and the end of the third month.

Table (1): Mean of WBC count response to Glivec.

WBC RESPONSE TO GLIVEC			
	Mean of WBC count/ml	Minimum	Maximum
At diagnosis	166,300	69,800	450,ooo
1st week	102,300	20,000	313,000
2ndweek	59,400	9.400	150,000
3rd week	31,000	4,200	98,000
4th week	12,500	2,500	69,000
6th week	9,800	2,600	35.600
8th week	6,900	2,700	24,000
12th week	6,700	1,900	18,800

Table (2): Compare between the mean of WBC count, Hb level and platelet count at the time of diagnosis and the at 3rd month. "P value calculated by chi square test".

Mean	At diagnosis	At 3rd month	" P value "
WBC count	166,300	6,700	0.000
Hb level	10.9	11.5	0.029
Platelet count	326,000	236,000	0.000

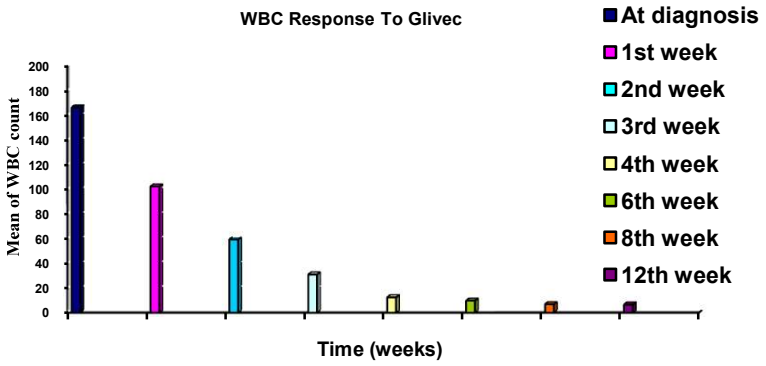

Figure (2): WBC response to Glivec.

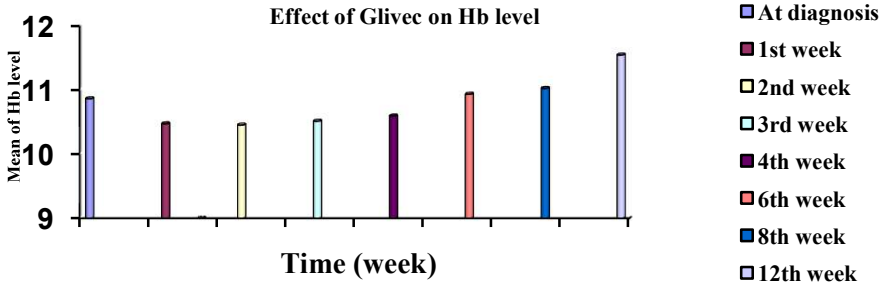

Figure (3): Effect of Glivec on Hb level.

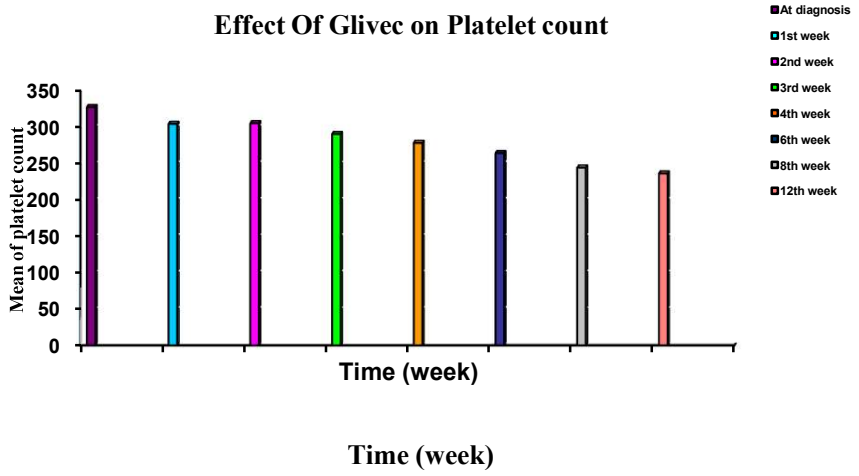

Figure 4. Effect of Glivec on platelet count.

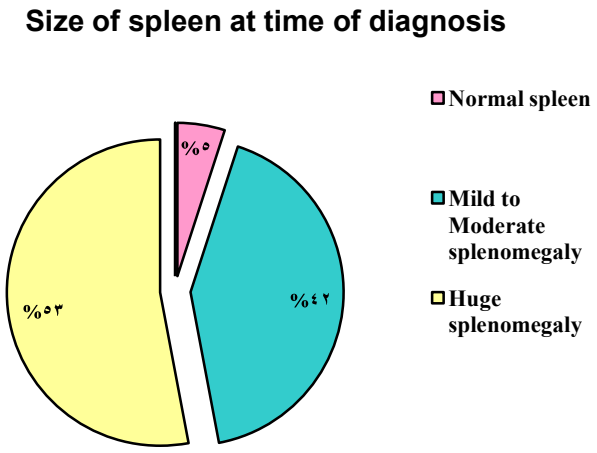

Figure (5): Spleen size at the time of diagnosis.

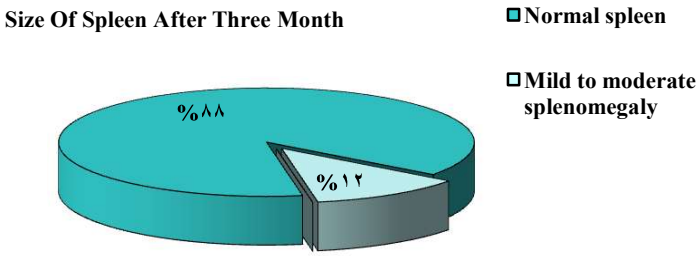

Figure (6): Spleen size after three month.

Discussion:

Chronic myeloid leukemia has an incidence of 1 to 2 cases per 100,000 people per year [9, 10]. The median age of patients at presentation is 50 to 55 years. The incidence is slightly higher in males than in females [11]. It is reported that the CML occurs more often in men than in women with a ratio 1.5:1 [12].

In the present study we wanted to compare the above facts, set for the developed world, with our own figures. The total number of chronic myeloid leukemia patients in this study is 67, the male: female ratio was 1.1: 1 (52% male and 48% female). There is no significant difference in the male: female ratio, compared with the 1.5: 1 in the literature [12]. Expectedly the male patients were slightly higher than female patients in our patients.

Although our number of patients were small and could not be statistically valid, but this is the general impression about this disease in Kirkuk - Iraq. In the current study the mean age of CML patients was 44 years as compared to 53 years in the world literature. The peak incidence of CML is between 41 to 50

years and only (15%) of patients were above 70 years of age. Certainly we are looking at a much younger population of patients with CML in our society with nearly ten years difference in age between our patients and those from the developed world. This issue has been raised in the past and it is well-known that CML in the Middle East affects a younger population [13].

The most important finding in the peripheral blood is neutrophil leukocytosis and basophilia. The leukocytosis ranges from 20,000/µL to more than 500,000/µL, with a mean ranges of 134,000 to 225,000/µL in most studies [14, 15, 16]. Myeloblasts do not usually exceed (3%) of the total WBC count. Platelet counts under 100,000/µL are very uncommon [14, 15, 17, 18]. Most patients have a normochromic/ normocytic anemia at the time of diagnosis, although normal or elevated hemoglobin levels are reported [14, 16].

It is reported that the presumptive diagnosis of CML can be made from the results of blood cell counts and examination of the blood film [14, 19, 20]. It was reported that the blood hemoglobin concentration is decreased in most patients at the time of diagnosis. The total leukocyte count is always elevated at the time of diagnosis and at least half of the patients have total white cell counts greater than 100,000/µL.

University of Rochester Medical Center did a study on blood count at the time of diagnosis in 90 cases of chronic myeloid leukemia [12]. Their mean results are very comparable to our current mean as presented in table (2).

Table (3): Compare blood smear abnormalities.

Parameters	Rochester Medical Center (Mean)	Present study (Mean)
Total patients number	90	67
WBC x1000/µL	160,000	166,300
Neutrophil %	38	34
Lymphocyte %	8	8.8
Monocyte %	8	6.4
Eosinophil %	2	7.8
Basophil %	3	8.9
Blast cell %	3	3.7
Promyelocyte %	4	4.3
Myelocyte %	12	17.6
Metamyelocyte %	7	7
Band form %	14	4
Hb gm/dL	10	10.9
Platelet $x10^9$/L	442	326

The initial WBC count of patients included in this study at the time of diagnosis were ranged from 69,800/µL to 450,000/µL with a mean value of 166,290/µL. while after treatment for three month with Glivec, the mean of WBC count reduced to 6,700/µL with range from 1,900/µL to 18,800/µL.

In this study the differential count of WBC in the peripheral smear show the following results at the time of diagnosis, the means of blast cells are (3.7%); promyelocyte (4.3%); myelocyte (17,6%); metamyelocyte (7%); band form (4%); neutrophil (34%); eosinophil (7.8%); basophile

(8.9%); monocyte (6.4%). while after treatment for three month with Glivec, the means changed significantly for blast cells (0%); promyelocyte (0%); myelocyte (0.4%); metamyelocyte (2.2%); band form (5%); neutrophil (51.2%); eosinophil (1.8%); basophile (0%); monocyte (2.7%).

The initial patients' hemoglobin at the time of diagnosis are ranged between 6.5 gm/dL to 14.8 gm/dL with a mean value of 10.9 gm/dL. While after treatment for three months with Glivec, the mean of Hb level increased to 11.5 gm/dL with range from 7.8 gm/dL to 14.5 gm/dL, which is insignificant as an effect of Glivec on Hb level.

The initial platelet count of the patients at the time of diagnosis are ranged from 76 $x10^9$/L to 932 $x10^9$/L with a mean value 326 $x10^9$/L, while after treatment for three month with Glivec, the mean of platelet count slightly reduced to 236 $x10^9$/L with range from 80 $x10^9$/L to 500 x 10^9/L.

It was found that at the time of presentation, the spleen varies in size, ranging from just palpable to a mass filling the abdomen. Approximately (50%) of patients had splenomegaly extending more than 10 cm below costal margin at the time of diagnosis. Spleen is quite firm and usually nontender, unless splenic infarction is present, and the notch can easily be palpable [(21)].

Cortes reported that splenomegaly was present in approximately (90%) of patients at diagnosis, but with medical care being sought earlier, the presence of splenomegaly at the time of diagnosis is decreasing in frequency [(20)].

In this study the percentage of huge splenomegaly in CML patients at the time of diagnosis is (53%) and mild to moderate splenomegaly is (42%), so totally about (95%) of CML patients have splenomegaly. Which are nearly normalized (88%) the percentage after three months from treatment with Glivec and that percents show significant response of patients with splenomegaly to the treatment with Glivec.

The early hematological response in this study is (92.5%) of all CML patients during first three months that compared with early hematological response results for (204) patients with CML at Hammersmith hospital is (98.5%) [(22)].

Conclusion:

- Glivec is the target therapy in the management of the chronic myeloid leukemia with Ph-positive chromosome.
- Complete hematological response that arises during the first three months after starting treatment with Glivec in more than (90%) of the CML patients including WBC count return to normal level and the size of spleen which is nearly normalized in (88%) of CML.
- The hematological parameters especially the WBC count return to normal level with good response to the Glivec.
- The clinical parameters including the size of spleen which is nearly normalized in (88%) of CML patients that initially started the treatment with Glivec.

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