IMATINIB MESYLATE IN IRAQI PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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Abstract:

Background: Chronic myeloid leukemia (CML) is a clonal proliferation of stem cells that is characterized by granulocytosis with granulocytic immaturity. The molecular abnormality involving the ABL gene on chromosome 9 and the BCR gene on chromosome 22 have been established as being the proximate cause of chronic phase CML.

Objective: To study the clinical, and hematological responses to imatinib mesylate and the main side effects in Iraqi patients with CML in the three phases of disease.

Methods: Three hundred and sixty two patients with CML were enrolled .they were diagnosed by peripheral blood and bone marrow aspirate examination and were treated with imatinib mesylate 400 mg/day as one single dose orally and followed up every 4 weeks for clinical , hematological responses and evaluation of side effects.

Results: The frequency of CML cases by residence was 17. 40%, 21.8% and 61.6% from south, north and middle regions of Iraq respectively. The age of patients ranged 14-70 years, 192 males (53%) and 170 females (47%). Complete clinical and hematological responses were observed in 325 (90%) of patients within 3 months from the initiation of imatinib in the chronic phase of the disease, only 4/10 responded in the accelerated phase at higher dosage of 600-800mg/day , no one in the blastic phase responded. Side effects were generally mild and tolerable.

Conclusion: Imatinib mesylate is effective and safe in achieving high clinical and hematological responses in chronic phase CML patients, but has poor response in accelerated and acute blastic phases. Side effects are generally mild.

Key words: Chronic Myeloid Leukemia, Imatinib Myseglate

IRAQI J MED SCI, 2007; VOL. 5 (2):78-84

Introduction

Chronic myeloid leukemia (CML) is a clonal proliferation of the stem cell, that is characterized by anemia,extreme peripheral blood granulocytosis and granulocytic immaturity, basophilia, often thrombocytosis and splenomegaly. The hematopoietic cells contain a reciprocal translocation between chromosome 9and 22 in over 90% of patients which leads to an overtly short, long arm of chromosome 22, referred to as Philadelphia (Ph1) chromosome(22q-) [1]. A rearrangement of the break point cluster region on chr.22 is probably present in all patients with CML and the molecular abnormality involving theABL gene on chr. 9 and the BCR gene on chr. 22 have been established as being the proximate cause of chronic phase CML [1,2].

The disease has a very high propensity to evolve into an accelerated or acute fatal phase resembling acute leukemia. The incidence in USA is 1-2 patients in 100000 of population [2]. Until recently the only treatment choices were, stem cell transplantation which, though curative, is limited to a small proportion of patients with CML, and hydroxyurea-based , or interferon -alfa (IFN) based regimen [4, 5].

Treatment with IFN has a deleterious effect on patients quality of life and is associated with physical toxicities as fever

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Relieved19th February 2006: Accepted 10th May 2006.

and chills, hypotension and fatigue, impaired memory and inability to concentrate [4-7]. Hydroxyurea is well tolerated but is of limited efficacy with no effect on disease progression or survival [8].

Imatinib mesylate is an oral targeted therapy, a selective Bcr- Abl tyrosine kinase inhibitor with significant activity in the treatment of Ph positive CML and in Ph +ALL patients [9]. In clinical trials [10-13], imatinib has demonstrated a high level of efficacy, clinically and hematologically in the three phases of the disease and is associated with significantly less toxicity, which is likely to translate into quality of life benefit and survival advantage [14].

In patients with CML chronic phase –(post IFN alfa failure), imatinib induced complete cytogenetic response in 48% and major cytogenetic response (Ph chromosome less than 35%) in 65% of patients. The two year transformation rate was 13% and the two year survival rate was 92%[10, 14].

In the International Randomized Study (IRIS) [13], comparing IFN and low dose Ara-c, versus imatinib in patients with newly diagnosed CML in chronic phase, Imatinib was associated with significantly better 18 months rate of complete cytogenetic response (7 versus 14%), respectively. In the most recent study, imatinib versus other therapies, imatinib was a significant independent favorable prognostic factor for survival [14].

Aim of this work

Is to study the clinical and hematological responses to, and the side effects of Imatinib in Iraqi patients with chronic myeloid leukemia in the three phases of the Disease and to highlight some aspects of the epidemiology of this disease in this country.

Patients and methods

Late in 2002, a committee was assigned by the Ministry of Health to help delivering imatinib (glivec) to Iraqi CML patients and the National Center for the Treatment of Blood Disorders (at Al-Mustansiriya University) was chosen for prescribing and dispensing this drug agent. At the time of starting writing the results of this work we had already seen 362 patients with CML who were diagnosed on clinical and hematological grounds by experienced physicians and hematologists.

Cytogenetics was unfortunately not performed because of technical difficulties. They were 53% males and 47% females with an age range of 14-70 years. Full investigations were performed for each including, CBC and ESR, Bone marrow aspirate, FBS and BU, uric acid and hepatic transaminases. There were no clear-cut exclusion criteria in this pilot study except patients with advanced organ failure.

The dose of imatinib was 400 mg to be taken orally in one single dose preferably after breakfast. Patients were instructed to attend every 4 weeks and report on a special sheet, their subjective body responses, daily activity and side effects, and to undergo careful physical examination for splenic size, jaundice, edema or any skin reaction, also to have their peripheral blood examined for Hemoglobin, WBC and differential count and platelet count to assess the hematological response and the disease phase.

Statistics

Parameters were represented as means& percentages on the figures.

Results

The prevalence of the CML in Iraq is about 2/100000, assuming the population is 25 millions and the No. of CML patients in mid 2005 was approaching 560 in the (NCH) center. Figure 1 shows that 51% of patients have an age range between 30-49 years and around 30% of the total were younger than 30 years.

Figure 2 shows no obvious difference in sex distribution, 53.07% males and 46.9% females. Figure 3 shows the distribution

according to the geographical area. North of Iraq: 21.9%, Middle 61.6% and the South 17.4%. Figure 4 shows the relationship to occupation, ordinary laborers were the commonest class and the farmers least affected! Figure 5 shows the Hb level before therapy. Figure 6 shows the WBC count 3 months after therapy. Figure 7 shows the response in accelerated phase. Figure 8 demonstrates the response in blastic phase.

Ten patients were in accelerated phase, four of them reverted to chronic phase on higher dose imatinib therapy. Six patients were in acute blastic phase and showed no response.

Table 1 shows the distribution of registered side effects of Imatinib in all patients treated. Side effects were generally mild and tolerable. Of the non hematological: muscle and joint pain seen in 325 patients (90%), nausea and indigestion in 304 patients (84%), peri orbital swelling and weight gain in 144 patients (40%). Of the hematological side effects. granulocytopenia grade 1,2: in 100 patients (30%), grade 3,4: in 28 patients (8%) and thrombocytopenia Grade 1,2: in 72 patients (20%), Grade 3,4: in 18 patients (5%).

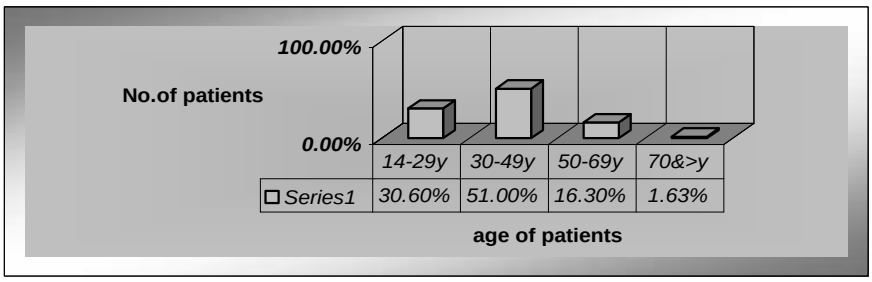

Figure 1: Age Distribution

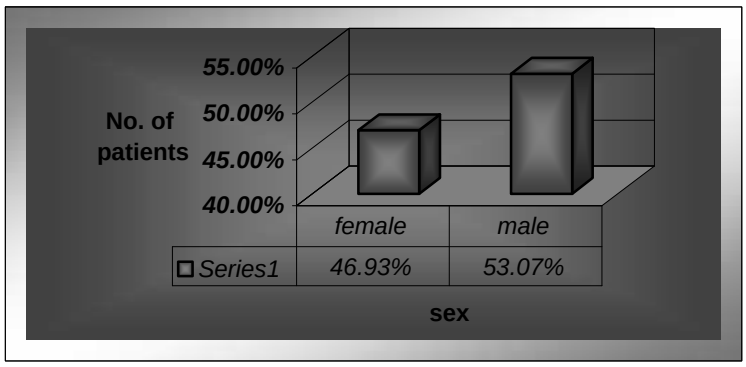

Figure 2: Sex distribution

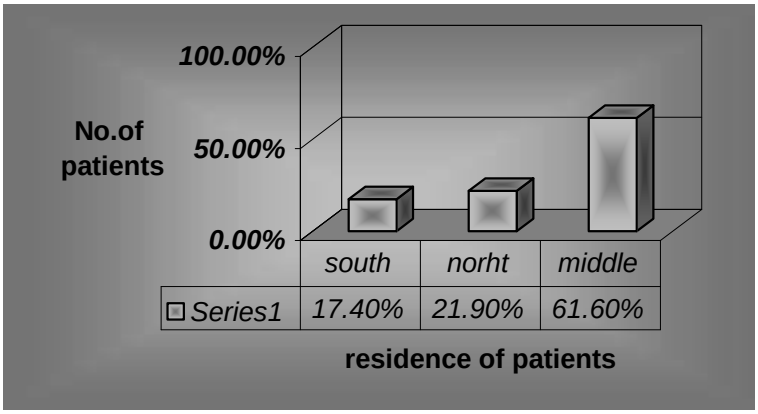

Figure 3: Residence

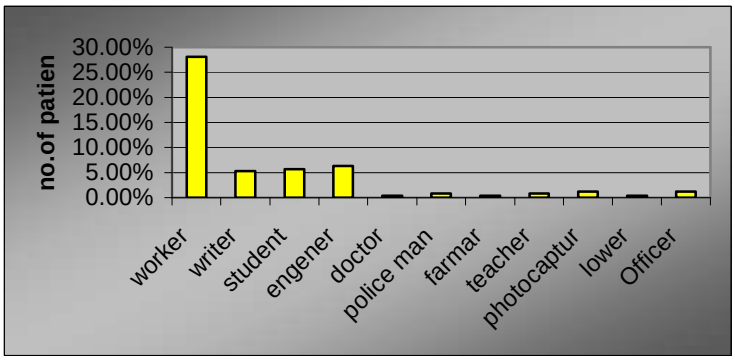

Figure 4: Occupation Of Patients

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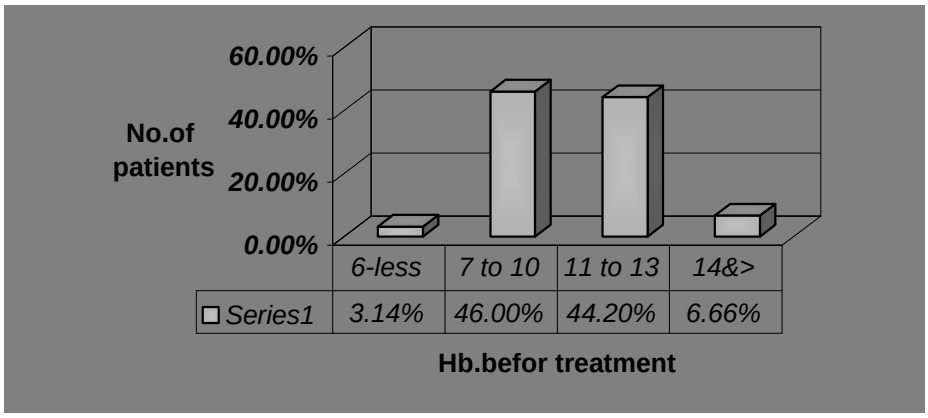

Figure 5: Hb concentration at presentation

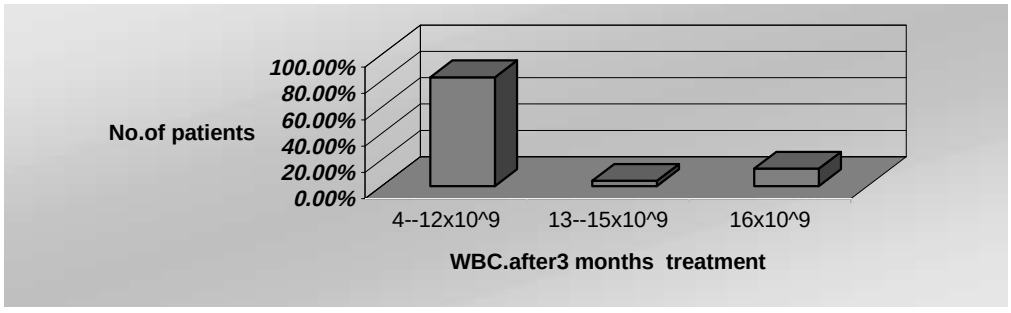

Figure 6 :WBC count after 3 months of treatment

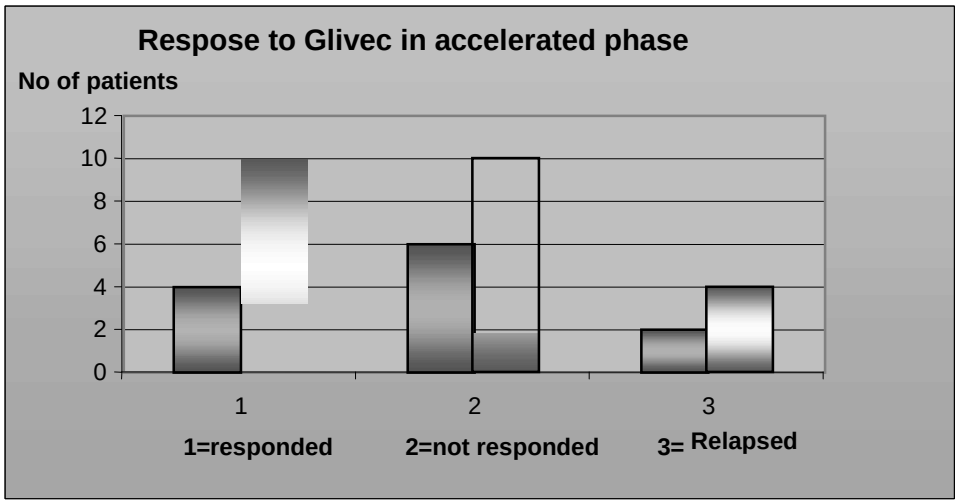

Figure 7: Response in accelerated phase

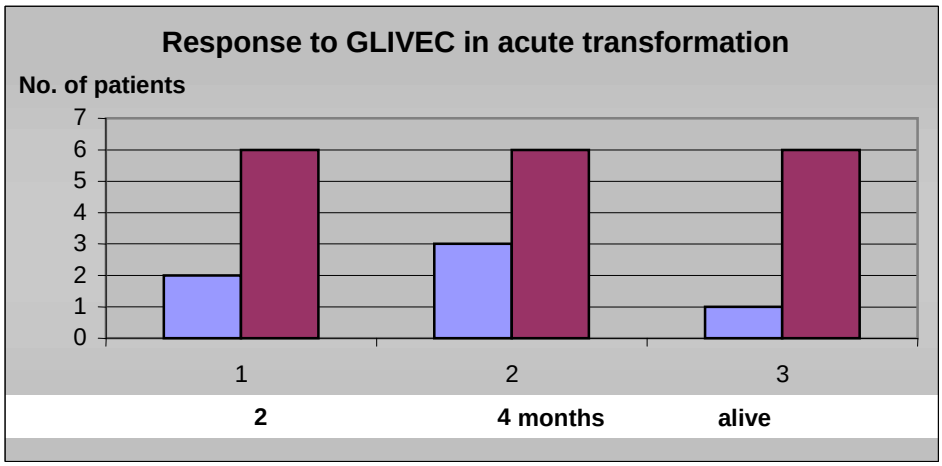

Figure 8: Response in blastic phase

Table 1: Side Effects of Imatinib

Side Effects	Very Common (› 1/10)	Common (› 1/100 ‹ 1 / 10)	Uncommon (‹ 1 /100 › 1/ 1000)
Infections			
Sepsis, pneumonia			+
H zoster & simplex			+
CNS			
Headache			+
Dizziness, Parasthesia, Epileptic fits			+
Eye			
Conjunctivitis			+
blurred vision		+	
Dry eye			+
periorbital swelling		+	
Ear			
Vertigo & Deafness			+
tinnitus			+

Cardiovascular			
hypertension, hypotension			+
palpitation, chest pain, dyspnoea			+
Gastro intestinal			
Nausea, dyspepsia	+	+	
vomiting			
Diarrhea & flatulence & constipation			+
Hepatic			
jaundice			+
increased SGPT & ALP			+
Skin			+
Dermatitis		+	
Facial oedema &eyelid oedema	+		
dryness & photosensitivity			
Musculo skeletal			
muscle pain & cramps	+		
joint swelling			+
bone pain, sciatica			+
Genitourinary			
renal insufficiency			+
gynaecomostia			+
menstrual disturbance			+
polyuria & polydepsia			+
Blood			
mild Neutropenia	+		
mild thrombocytopenia	+		
pyrexia & Rigor			+
Weight gain			
Early		+	
Later	+		

Discussion

The prevalence of CML in Iraq is approaching 2/100000 which is nearly the maximum figure found in the literature, 1-2/100000[1,2] By April 2005 the number of patients in the NCH rose to 545. Has the disease increasing in frequency or incidence in our country?. The answer may be (yes) in view of the environmental pollution which the country had been exposed to, over the past two decades and the hot issue of the depleted uranium and its adverse radiation effect. Another point is that chemicals and insecticides do not seem to be a causative agent for CML due to the emerging observation that farmers had the lowest rate of prevalence despite heavy exposure to these agents, this is also compatible with the literature that, chemicals or insecticides are not incriminated in CML development[1, 2].

Chronic myeloid leukemia is a killing disease in 3-6 years by progressing into accelerated or acute phase. Of the 362 patients enrolled in this study 289(80%) are alive and in hematological remission at the time of reporting i.e., two and a half years from the start of imatinib.

This is consistence with the results of several previous cohorts in the world[8-11,14]. With regard to the age, about 30%of patients were under the age of 30 years and 81% under the age of 49 years, this may give an impression that CML is not a disease of middle aged population, but probably if a larger number of patients were enrolled it would have shown different results.

Twenty patients developed accelerated or blastic transformation during the past two years after they were

previously in remission on imatinib, most of them have had the disease for more than 4 years. This may be attributed to the development of resistance perhaps due to a mutation at the BCR-ABL that reduce the binding affinity of imatinib as it has been reported lately [15].

Side effects were mild in the majority of our patients, both the hematological and the non hematological which is consistent with the results of several previous studies[16]

Conclusion

Imatinib mesylate induces good and durable clinical and hematological response in patients with chronic phase CML with acceptable mild side effects. Patients with accelerated phase and those in blastic crises showed poor response.

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