Original Article

Comparison of effectiveness and safety of Iranian-made vs. Indian-made imatinib in treatment of chronic myeloid leukemia

Kamran Moshfeghi, Neda Nazemzadeh[1], Valiollah Mehrzad[2], Alireza Hajiannejad[3], Farah Esmaili[4]

Departments of Hematology and Oncology and [1]Internal Medicine, Arak University of Medical Sciences, [2]Departments of Hematology and Oncology, [3]Cardiac Medicine and [4]Internal Medicine, Isfahan University of Medical Sciences, Iran

Abstract

Background: Currently, imatinib is the drug of choice for initiation of medical treatment of chronic myeloid leukemia (CML) in the chronic phase. The current study was carried out to compare effectiveness and safety of Iranian vs. Indian imatinib.

Materials and Methods: The clinical study was performed on newly diagnosed CML patients in Seyyed-oShohada Hospital (Isfahan) and Khansari Hospital (Arak) from January to June 2011. The control group consisted of CML patients who received Indian imatinib previously. The drug was initiated with the dose of 400 mg daily. The patients were followed for six months, and the treatment outcomes (WBC $<10^4$) and molecular response. Finally, the two groups were compared in these respects.

Result: We evaluated 43 patients in each group. The hematological and molecular responses for the Iranian Imatinib were respectively 86.0% and 46.5%, while the rates were respectively 86.0 and 44.2% for the Indian imatinib. The two groups were similar with regard to the treatment outcome. The two groups were not significantly different with regard to the drug adverse effects.

Conclusion: According to the findings, the Iranian imatinib is not different from the Indian drug in the hematological and molecular responses in treatment of the chronic phase of CML patients. Furthermore, the adverse effects of the two kinds were not significantly different. Compared with the results of other studies, the effectiveness of Iranian imatinib is equivalent to the Indian drug can be employed for treatment of CML patients in the chronic phase.

Key Words: Chronic myeloid leukemia, effectiveness, imatinib, safety, treatment

Address for correspondence:
Dr. Neda Nazemzadeh, Department of Internal Medicine, Arak University of Medical Sciences, Iran. E-mail: dr.nazemzade@gmail.com

Received: 15.04.2012, **Accepted:** 05.08.2012

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.108000

INTRODUCTION

Myeloid leukemia is a heterogeneous group of diseases, defined by infiltration of neoplastic cells of the hematopoietic system in blood, bone marrow, and other tissues. If not treated, different types of leukemia range from severely fatal types to slow growing ones.[1] Considering the diversity of alternatives present for the treatment, making decision about treatment of CML is complex. The choices include probability

How to cite this article: Moshfeghi K, Nazemzadeh N, Mehrzad V, Hajiannejad A, Esmaili F. Comparison of effectiveness and safety of Iranian-made vs. Indian-made imatinib in treatment of chronic myeloid leukemia. Adv Biomed Res 2013;2:17.

of definite treatment by allogenic hematopoietic cells transplantation (HCT), disease control and definite treatment using tyrosine kinase inhibitors, and palliative treatment using cytotoxic drugs. Since allogenic HCT have resulted in many cases of toxicity and treatment by imatinib has promising results, treatment of CML is a rapidly evolving field. Therefore, experience of the physician and preference of the patient are involved in selecting the therapeutic approach. Currently, the goal of treatment in CML is achieving permanent and prolonged non-neoplastic non-clonal hematopoiesis accompanied by eradication of any remaining cells containing BCR/ABL copy. Therefore, the goal is complete molecular remission and cure.[2]

Imatinib is a tyrosine kinase inhibitor, which has been used as an effective treatment for CML patients from almost ten years ago. Considering the relative specificity and limited adverse effects of imatinib, and also considerable improvement of CML patients, when imatinib was introduced to the global medicine market, it has been approved by the Food and Drug Administration (FDA) as the standard treatment of CML.[3] Before introduction of imatinib, CML patients who were not candidate for bone marrow transplantation received alpha interferon together with cytarabine. However, recent clinical trials have indicated the significantly higher effectiveness of imatinib.[4] After manufacturing imatinib in Iran in 2010, the Iranian insurance companies do not support the Indian-made kind of the drug. So far, no studies have been performed on comparison of the effectiveness of Iranian-made vs. Indian-made imatinib. Therefore, it was needed to evaluate the effectiveness of the Iranian kind of the drug. As a result, by comparing the Iranian kind with the Indian kind of imatinib, we could obtain equivalent or higher effectiveness and safety at lower costs.

MATERIALS AND METHODS

This clinical trial was performed on CML patients in the chronic phase. The participants were selected from among the new cases of CML (ph+) who referred to the hematology clinics of Seyyed-o Shohada Hospital (Isfahan) and Khansari Hospital (Arak) from January to June 2011. The control group consisted of CML patients who previously received Indian-made imatinib. Diagnosis of the disease was based upon clinical suspicious followed by peripheral blood and bone marrow studies. Moreover, the diagnosis was confirmed by genetic studies for detection of Philadelphia chromosome and RT-PCR for detection of BCR-ABL gene. The exclusion criteria were having fatal accompanying diseases, moderate to severe renal failure (GFR <40), moderate to severe hepatic failure (Child B or C), and CML patients in the accelerated and blastic phases. The cases were selected using non-randomized consecutive sampling. In previous studies, the hematological effect of imatinib was reported as 0.9, and we expected to obtain 85% cure in the Iranian kind of imatinib. With regard to these rates and considering the alpha error value of 0.05, test power of 80%, and using the equation for comparison of two ratios, the sample size was calculated as 86 patients for the two groups (43 patients in each group). Before initiation of the study, all patients signed an informed written consent. During the study, the researchers followed the ethical principles of the Declaration of Helsinki and the 24 items considered in the ethical guideline of the Iranian Ministry of Health.

Imatinib was started at the dose of 400 mg daily, and if appropriate treatment response was not obtained, the dose was gradually increased to 800 mg daily, if it was tolerated by the patients. In the first month of the study, the patients were visited on a bi-weekly basis by the author, under supervision of the attending physician of the hematology clinic, and the patients' datasheet were filled out during the visits. For the participants, all tests were ordered bi-weekly in the first month of the study, and then monthly. Liver and kidney function tests and serum level of electrolytes were monthly measured. Common adverse effects of the drug (according to previous studies) were evaluated in the visits. These adverse effects were

1. cardiovascular complications including water and salt retention, and pleural and pericardial effusion
2. the drug influence on the central nervous system (CNS) including fatigue, headache, anxiety, and depression
3. unwanted effects on the gastrointestinal (GI) system including nausea, vomiting, diarrhea, and abdominal pain
4. hematological complications including hemorrhage, neutropenia, decrease platelet count, and anemia;
5. hepatic toxicity including elevated liver enzyme levels and increased bilirubin level; and
6. reduced kidney function.

During the visits, if non-hematological complications such as hepatic complications (Bil ≤ X2.5, LFT ≤ X5) occurred, the drug was discontinued, and then when liver indices returned to normal (Bil ≤ X1.5, LFT ≤ X2.5), the drug was again administered at a lower dose. If hematological complications occurred (ANC $<1 \times 10^3$ or Plt $\leq 50 \times 10^3$), the drug was discontinued and then when the complications subsided, the drug was started with the previous dose, and if the hematological complications occurred again, the drug was initiated at a lower dose.

The data was collected according to a checklist of complications. Hematological response was defined as the WBC count below 10^4, accompanied with platelet count decrease to lower than 450×10^3. Moreover, presence of BCR-ABL gene was detected by RT-PCR to determine the level of molecular response.

During the study, 43 patients were evaluated in the Iranian kind group, and the same number of patients was studied in the Indian kind group. Among the patients, 51 were male. The mean age of participants was 60 years. During the treatment, WBC count similarly decreased in the two groups, and the two groups were not different in this respect (from the mean number of 106000 and 99348 in the first week to 6160 and 6572 in 24 week in the Iranian kind and Indian kind groups, respectively). In each group, the WBC count of six patients did not reach below 10^5 until 12 week of treatment. The hematological response in both groups was 86.0%. In one patient in the Iranian kind group, as the drug dose was increased after 12 week, WBC count decreased from 61500 to 7120 in 16 week, and in one patient in the Indian kind group, as the drug dose was increased after 12 week, WBC count decreased from 20370 to 2350 in 16 week [Figure 1].

The platelet count decreased similarly in both groups during the treatment course (from the mean number of 354444 and 444216 in the first week to 254205 and 249880 in 24 week in the Iranian kind and Indian kind groups, respectively) ($P < 0.001$). Also, the hemoglobin (Hb) level increased in the two groups similarly (from the mean level of 12.1 and 11.8 in the first week to 12.9 and 12.8 in 24 week in the Iranian kind and Indian kind groups, respectively) ($P < 0.001$). The two groups were not significantly different with regard to the decrease in the platelet count and increase in the Hb

Table 1: Baseline characteristics in the study groups

	Iranian *N*=43	Indian *N*=43	*P*
Age			
<40	3	4	0.789
40~50	10	10	
50~60	13	14	
>60	17	15	
Female/Male	17/26	17/26	_
WBC	101384.42±178214.81	98886.05±63841.85	0.931
Platelets	354444.19±257803.91	444216.28±426233.90	0.241
Hemoglobin	12.15±1.71	11.88±1.85	0.482
AST	24.32±6.34	25.48±9.79	0.516
ALT	18.55±5.19	20.11±6.21	0.211
ALKP	208.39±56.66	237.72±81.89	0.057
Bilirubin	0.74±0.22	0.71±0.29	0.650
BUN	15.00±2.56	14.18±2.91	0.173
Creatinine	0.64±0.18	0.75±0.18	0.006

Data are presented as mean±SD or number (%); WBC: White blood cells, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALKP: Alkaline phosphatase, BUN: Blood urea nitrogen

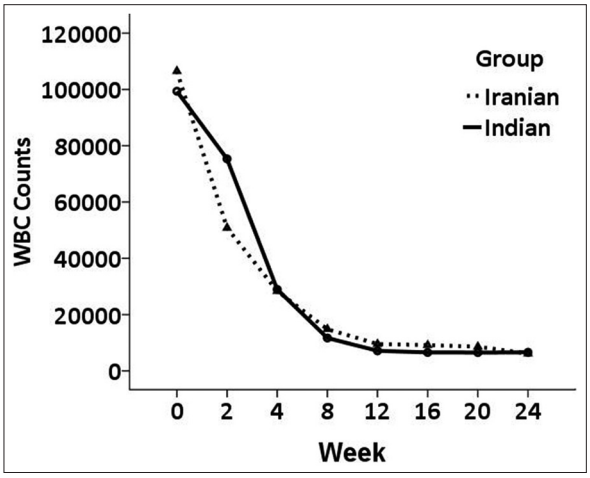

Figure 1: WBC count changes in the groups treated with Iranian and Indian imatinib

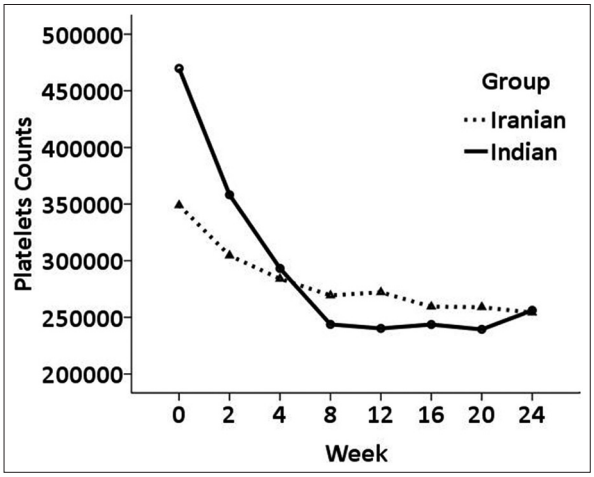

Figure 2: PLT count changes in the groups treated with Iranian and Indian imatinib

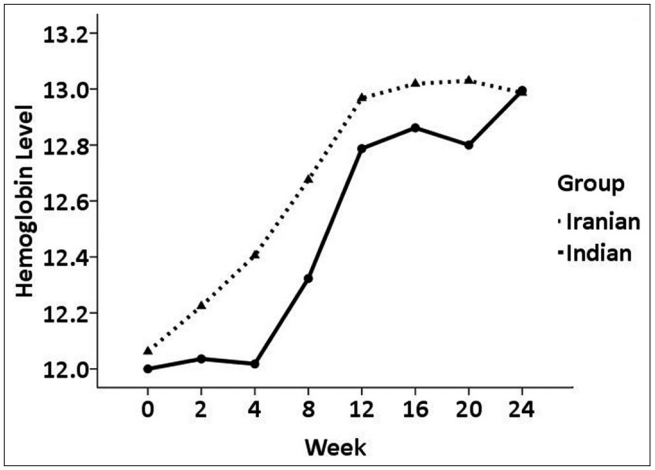

Figure 3: Hb count changes in the groups treated with Iranian and Indian imatinib

level ($P > 0.05$) [Figures 2 and 3].

Presence of BCR-ABL gene before and after the intervention in both groups is given in Table 1-3. As it is observed, frequency of BCR-ABL gene after the intervention decreased 50% in both groups ($P < 0.001$), and the two groups were not different in this respect ($P > 0.05$).

Liver enzyme levels did not increase in any patients of the two groups. In the Iranian kind group, from one to 24 week, the mean level of AST decreased from 24 to 20, for ALT from 18 to 15, and for alkaline phosphatase (Alk P) increased from 208 to 211. This is while in the Indian kind group, from one to 24 week, the mean level of AST decreased from 25 to 19, the mean level of ALT decreased from 20 to 15, and the mean level of ALK P decreased from 237 to 211. The mean level of bilirubin in one week and 24 was 0.7 for both groups. After the treatment course, the BUN level increased 1.1 on average in the Iranian kind group, while the level did not significantly increase in the Indian kind group. Moreover, after the course of treatment, the creatinine level increased on average 0.07 in the Iranian kind group, while there was not a significant increase in the Indian kind group. However, we did not observe renal complications in the Iranian kind group, and the increase lied within normal range, although it was statistically significant. The serum electrolyte levels after the treatment did not significantly change in both groups ($P > 0.05$). Comparison of the two groups with regard to the cumulative frequency of each adverse effect is provided in Table 2. As it is shown, the commonest adverse effects of the two kinds of the drug were edema (facial edema was more prevalent) (62.7 and 63.7% in the Indian and Iranian kinds, respectively), GI symptoms (41.9 and 39.1% in the Indian and Iranian kinds, respectively), fatigue and headache (40.6 and 43.2% in the Indian and Iranian kinds, respectively), mood symptoms (11.6 and 15.6% in the Indian and Iranian kinds, respectively), and hematological complications (9.3% in both kinds). The two groups were not significantly different in the total frequency or cumulative frequency of the adverse effects ($P > 0.05$).

Table 2: Changes in the frequency of BCR-ABL gene before and after the intervention in the two groups

	Iranian kind	Indian kind	*P**
Positive for BCR-ABL gene			
At the beginning	43 (100)	43 (100)	-
24 week	23 (53.4)	25 (55.8)	0.500
*P***	<0.001	<0.001	

Data are shown as number (%), *Chi-square Test, **McNemar test

DISCUSSION

In the current study, the effectiveness and safety of the Iranian kind of imatinib was evaluated. As a result, by comparing the Iranian kind with the Indian kind of imatinib, the possibility of replacement of the Indian kind of the drug with the Iranian kind and at lower costs was investigated. According to the findings, the changes in WBC and platelet counts during the six-month course of the treatment were similar for the two kinds. Furthermore, the two groups were similar with regard to the molecular findings. The two groups were not significantly different in prevalence of hepatic and renal toxicity. These findings demonstrate the equivalent effectiveness of the Iranian kind of the drug with the Indian kind in treatment of chronic phase of CML.

In the study, the hematological response after three

Table 3: Comparison of the two groups in cumulative frequency of adverse effect of Iranian and Indian imatonib

Adverse effects	Iranian kind		Indian kind		*P**
	Total frequency (%)	Median (range)	Total frequency (%)	Median (range)	
Edema	62.7	2 (0 to 6 times)	62.7	2 (0 to 6 times)	>0.05
Pleural effusion	0	0	0	0	-
Pericardial effusion	0	0	0	0	-
Left ventricular dysfunction	0	0	0	0	-
Cardiogenic shock	0	0	0	0	-
Fatigue	45.8	0 (0 to 4 times)	41.8	0 (0 to 4 times)	>0.05
Headache	39.5	0 (0 to 2 times)	39.5	0 (0 to 2 times)	>0.05
Anxiety/depression	15.6	0 (0 to 5 times)	11.6	0 (0 to 5 times)	>0.05
Nausea	40.1	0 (0 to 2 times)	44.1	0 (0 to 2 times)	>0.05
Diarrhea/vomiting	41.1	0 (0 to 2 times)	44.1	0 (0 to 2 times)	>0.05
Abdominal pain	38.5	0 (0 to 2 times)	39.5	0 (0 to 2 times)	>0.05
Hemorrhage	0	0	0	0	-
Neutropenia	9.3	0 (0 to 3 times)	9.3	0 (0 to 3 times)	>0.05
Platelet count decrease	9.3	0 (0 to 4 times)	11.6	0 (0 to 4 times)	>0.05

Data are shown as Median [range], *Mann-Whitney U Test

months of treatment was 86.0% in both groups, which remained unchanged until the sixth month of treatment. Furthermore, at the end of the treatment course, frequency of BCR-ABL gene decreased approximately 50% in both groups; such that the molecular response was 46.5 and 44.2% in the Iranian and Indian kinds of the drug, respectively. This shows that the Iranian-made imatinib had effectiveness similar to the Indian kind of the drug.

To compare the results obtained with the findings of other studies such as the IRIS clinical trial,[5] in the 18-month follow up, complete hematological and major cytogenetic responses were observed in 97 and 87% cases, respectively,[6] while complete cytogenetic response and major molecular response (absence of BCR-ABL in PCR examination) were respectively observed in 76 and 39% of patients who received imatinib.[7] In another clinical trial,[8] in a five-year follow up, the rates of complete cytogenetic and major molecular responses were respectively 83 and 50%, and the five-year survival rate was 83%. Our findings were in agreement with the results of these studies. In another study carried out in Tehran by Razavi *et al*., on the Indian-made imatinib, the rates of hematological cure, and complete and partial cytogenetic recovery were reported as 90, 46, and 43%, respectively.[9] Our results are consistent with their findings.

None of the patients in the study experienced drug-induced hepatic or renal toxicity. Although after the treatment, liver enzyme levels in both groups significantly decreased (3.9 and 5.8 for AST, and 2.7 and 5.0 for ALT in the Iranian and Indian kind groups, respectively), the changes were not clinically important. Moreover, after the treatment course, the mean levels of BUN and Cr increased on average 1.1 and 0.07 respectively, which were again clinically insignificant. The serum levels of electrolytes after the treatment did not significantly change in the two groups. Frequency of common adverse effects observed for the Indian and Iranian kinds of the drug in the study were as follows: edema (facial edema was more prevalent) (62.7 vs 63.7%), GI symptoms (41.9 vs 39.1%), fatigue and headache (40.6 vs 43.2%), mood symptoms (11.6 vs 15.6%), and hematological complications (9.3% in both kinds). In the study, no case of drug discontinuation owing to drug adverse effects occurred. In other studies, the adverse effects were reported to be mild to moderate, and drug adverse effects leading to discontinuation of the treatment was reported in few cases (approximately 2%). The most prevalent adverse effects in previous studies were edema, nausea, cramp, rash, and diarrhea, which occurred in 29-60% of the patients. Moreover, neutropenia of grade 3 and 4, leukopenia, thrombocytopenia, or anemia have been reported in 7 to 35% of the patients.[10] In the IRIS clinical trial, 1% of the patients were reported to be unable to tolerate imatinib.[11] This is while in another study, imatinib was discontinued for 25% of the patients because of not being tolerated.[8]

Currently available evidence indicates that increasing the dose of imatinib in the patients, in whom cytogenetic response is not developed, can be helpful. However, this is less effective for patients without hematological response or those who do not have favorable molecular response.[9] For instance, in the present study, increase in the drug dose resulted in hematological response after three months of treatment only in one patient.

The study had some limitations. The course of treatment and follow up was six months. It is suggested that in future studies in the country, the time interval be extended. Moreover, we defined molecular response as response or lack of response, and it is necessary to evaluate the response qualitatively.

CONCLUSION

According to the results obtained, the Iranian-made imatinib was not different from the Indian-made imatinib in the hematological or molecular responses in treatment of CML patients in the chronic phase. Moreover, the two kinds of the drug were not different in terms of adverse effects. Comparing our results with those obtained in other studies, it can be concluded that Iranian-made imatinib could be used in treatment of CML patients in the chronic phase. It is suggested that the patients participated in the study be followed for longer times. Carrying out further studies on patients who do not respond to the conventional dose of imatinib and also initiation of treatment at higher doses of the drug is recommended.

REFERENCES

1. Cervantes F, Mauro M. Practical management of patients with chronic myeloid leukemia. Cancer 2011;117:4343-54.
2. Fullmer A, Kantarjian H, Cortes J, Jabbour E. New developments in the treatment of chronic myeloid leukemia and Philadelphia-positive acute lymphoblastic leukemia. Leuk Lymphoma 2011;52:81-91.
3. Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood 2005;105:2640-53.
4. Marin D. Current status of imatinib as frontline therapy for chronic myeloid leukemia. Semin Hematol 2010;47:312-8.
5. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
6. Kantarjian HM, Cortes JE, O'Brien S, Giles F, Garcia-Manero G, Faderl S, et al. Imatinib mesylate therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: High incidence of early complete and major cytogenetic responses. Blood

2003;101:97-100.
7. Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-32.
8. de Lavallade LH, Apperley JF, Khorashad JS, Milojkovic D, Reid AG, Bua M, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: Incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 2008;26:3358-63.
9. Razmkhah F, Razavi M. Hematologic and molecular responses to generic imatinib in patients with chronic myeloid leukemia. Lab Med 2010;41:547-50.
10. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. J Clin Oncol 2003;21:1637-47.
11. Hahn EA, Glendenning GA, Sorensen MV, Hudgens SA, Druker BJ, Guilhot F, et al. Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: Results from the IRIS Study. J Clin Oncol 2003;21:2138-46.

Source of Support: Arak University of Medical Sciences, **Conflict of Interest:** None declared.