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Evaluation of the outcomes in patients with chronic myeloid leukemia treated with imatinib in 18-year follow-up

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ABSTRACT

The objective of this paper is to examine the effects of Imatinib on patients who are at the chronic phase of chronic myeloid leukemia (CML). **Method:** Totally, 79 patients with CML who received the treatment between 2003 and 2020 entered the study. The patients were evaluated in terms of molecular response rate and overall survival (OS). **Results:** About 75.9% of patients achieved deep molecular response in mean follow-up of 89.92 months. The OS rate was about 91.2%. **Conclusion:** There was no considerable cumulative toxicity with Imatinib long-term use. A high percent of patients had a deep molecular response.

1. Introduction

Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder with increased proliferation of granulocytes without losing cell differentiation and maturation. This disorder accounts for 15–20% of leukemia [1]; and its prevalence is about 10–15 cases per 100,000 people without any considerable difference based on genetic differences or geographical location. Average age of diagnosis is about 60–64 years [2, 3]; while the disease may appear in all of age groups [4]. It is estimated that by 2020, there will be 8540 new cases of CML and 1139 concomitant deaths in the United States [2]. The majority of people with CML have no symptoms when it is diagnosed. The disease is mostly diagnosed during routine check-ups or when CBC diff is tested for a non-related health problem. Clinical presentations of patients may vary based on the disease phase (chronic phase, accelerate phase, Blastic phase). The common symptoms and signs of the chronic phase include fatigue, weight loss, losing energy and power, heavy sweating, early satiety, and splenomegaly (45–50%). Accelerated or blast phases are diagnosed with signs and symptoms including petechial hemorrhage and ecchymosis caused by thrombocytopenia. Moreover, bone pain and fever may be the symptoms seen in accelerated or blastic phases. Anemia and progressive splenomegaly are other signs of blast crisis. About 90% of the patients are in the chronic phase [3]. The CML is diagnosed based on the peripheral blood and bone marrow findings and Philadelphia chromosome positive (9–22 translocation) in peripheral blood or bone marrow and FISH test showing transcript (BCR/ABL) [5, 6]. There is a need to do bone marrow cytogenetic to test more additional chromosomic abnormalities. Cytogenetic analysis is usually performed on a bone marrow aspiration sample under the following conditions: at the time of diagnosis, failure to achieve an appropriate molecular response based on the guideline, and any clinical and laboratory sign that indicates a loss of major molecular response. Mutational analysis is another test that may be done during follow-up. The BCR-ABL1 kinase domain mutation analysis is performed under the following conditions: failure to reach the major molecular response (MMR), loss of pre-existing MMR, and disease progression to accelerated or blastic phase [7, 8]. Accelerated or blastic phases may be initiated due to transcript (BCR/ABL)-dependent factors such as point mutations, which is because of resistance to tyrosine kinase inhibitors or factors irrelevant to BCR-ABL such as extra cytogenetic aberrations, which creates clonal evolution [9,10]. Positive BCR/ABL cells are genetically unstable and this may result in changes in the chronic form into acute form of the disease [11, 12]. Imatinib is the first inhibitor of tyrosine kinase that stops the tyrosine kinase generated by Philadelphia chromosome [13]. A dose of 400 mg is prescribed in chronic phase. It is essential to test molecular response; particularly within the first 12-month period of treatment with tyrosine kinase inhibitor (TKI). Measurement time of molecular response (MR) is important and is done in the 3rd and 6th months as well as after 12 months of treatment [14]. There are several guidelines to evaluate Imatinib-based treatment response in CML patients. According to European Leukemia

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Net (ELN), if BCR/ABL is above 10% in the first six months, treatment should be changed [15, 16]. A deep molecular response (DMR) is defined as BCR/ABL level of 0.01–0.000(1S). Cutoffs with various levels have been recommended. The MR^4, $MR^{4.5}$, and MR^5 molecular responses are at 0.01, 0.0032, and 0.001% levels respectively [17]. A significant percentage of patients reach a DMR. Discontinuation of treatment may be considered in individuals with sustained DMR (at least five years), especially if there is a possibility of accurate monitoring and excellent laboratory evaluations. The Stop Imatinib (STIM) showed that after discontinuation of treatment, molecular recurrence occurred in a number of patients [18]. Currently, discontinuation of TKI treatment for chronic phase with a DMR is a standard practice [19]. This paper is aimed at examining the effects of Imatinib on CML patients during a long-term follow-up. Molecular Remission Rate of studied medicine and Sokal Score of patients were examined to find out how many of patients had to switch to another medicine or entered another disease phases.

2. Methods and materials

This study was conducted on the patients who were diagnosed with CML and under treatment and needed Medical Oncology Clinic tests from 2003 to 2020. The patients were diagnosed based on the principles of European Leukemia Net (ELN) and 79 patients were selected as participants. Response to treatment was evaluated using molecular method. Patients with an inappropriate molecular response or disease progression from chronic phase to accelerated phase or blast phase were selected as candidates for BCR-ABL1 KD mutational analysis and cytogenetic analysis of bone marrow aspiration. Unfortunately, these tests are not affordable for Iranian due to its high cost. Other specifications of the patients including age, gender, diagnosis and treatment date, molecular test time, time of medicine switch and overall survival of patients from diagnosis to death or survival duration (if alive) were extracted from files and added to a checklist for statistical calculations. Sokal score of patients were calculated and analyzed according to the associated guideline [20]. The association between Sokal score and possible switch of medicine and survival was also tested. A daily dose of 400 mg of Imatinib was prescribed for all of cases.

3. Results

Totally, 79 patients with CP-CML were tested. Demographic and laboratory characteristics of the cases are reported in Table 1. Accordingly, the mean age of the cases was 41 yr with minimum and maximum age of 15 yr and 71 yr respectively; and 42 cases (53.2%) were men. Children were not included. Average size of spleen was about 15.8 cm and the minimum and maximum sizes were about 13 cm and 24 cm respectively. Minimum number of white cells was equal to 16.4×10^6/L; the highest cellular count was equal to 670×10^6/L and mean counted cells was equal to 1182×10^6/L cells. Minimum platelet count was equal to 58×10^6/L; the maximum rate was about 1394×10^6/L platelets, and average count was equal to 402×10^6/L platelets (Table 1). The side effects of Imatinib are listed in Table 2.

3.1. Treatment response evaluation

Unfortunately, treatment response evaluation using molecular method had not been performed routinely (after three, six and twelve months of treatment) by the majority of patients due to financial problems. Out of 79 patients, only seven (8.9%) had been tested more than once within three, six, 12, 18-month intervals after disease diagnosis based on the molecular response evaluation. The mean number of molecular evaluation in this group was about 5.7 times with minimum and maximum numbers of evaluations equal to four and six respectively. The rest of the cases ($n = 72$) were tested in different time intervals after being diagnosed and receiving treatment. Molecular response evaluation was done for 72 cases after entering the research plan. This molecular evaluation was done for these patients within 30 days. Table 3 indicates the results of molecular method-based treatment response of 79 patients. The mean follow-up time for 79 patients was about 89.92 ± 49.76 months. About 84.7% of patients had molecular response less than 1% and about 75.9% had molecular response about DMR. Molecular response in 14 patients out of 79 was as follows: molecular response of two patients was at the range of 10–100%(IS); eight patients had less than 10% (IS) molecular response; two patients had less than 1%(IS) molecular response, and two patients had molecular response of 0.0% (IS).Out of 14 patients who had switched treatment to Nilotinib, 12 cases had undesirable molecular response and two cases did not tolerate the previous treatment (these two patients had a desirable molecular response). The molecular response in the remaining 65 out of the 79 patients is listed in Table 3.

The mean follow-up time to medication change was about 69.67 ± 33.53 months (minimum 30 and maximum 138 months) with a median of 60 months. One patient out of 14 cases died from Cerebral Vascular Accident during follow-up period after the medicine switch, despite the suitable molecular response to the alternative medicine (Nilotinib). The patient who died of a Cerebral Vascular Accident was 65 years old and the cause of the Cerebral Vascular Accident was not clear; it might have been due to the side effects of the drug. Another case died after having acute myeloid leukemia (AML). The patient goes to the clinic for a visit

Table 1
Demographics and disease characteristics at baseline.

Sex no (%) Male: 42(53.2&), Female: 37(46.8%)	
Age at CML diagnosis (Year); Mean ± SD: 41.66 ± 14.09	
Median	41
15–71	Range:
Duration of follow-up (Month): Mean ±SD 89.92±49.76	
Median:	88
Range:	19–221
WBC:	
Mean × 103/uL ±SD	118×10^6/L ± 108,798.87
Median × 103/uL	81×10^6/L
Range × 103/uL	16×10^6/L -670×10^6/L
Hemoglobin	
Mean gr/dL ± SD	11.08 ± 1.57
Median gr/dL	11
Range gr/dL	7.6–15
Platelet count	
Mean × 103/uL ± SD	402×10^6/L ± 241,349.92
× 103/uL	58×10^6/L -1394×10^6/L
Median× 103/uL	328×10^6/L
Spleen size (%) Normal	16(20.3)
Mild	31(39.2)
Moderate	23(29.1)
Sever	9(11.4)

Table. 2
adverse side effects in our patients in CP treated with imatinib.

Side effect	All grade (number %)	Grade 1/2 (number%)	Grade ¾(number %)
Diarrhea	4(5%)	4(0.0%)	0(0.0%)
Constipation	4(5%)	3(3.75%)	1(1.25%)
Muscle cramps	6(7.5%)	6(7.5%)	0(0.0%)
Nausea	0(0.0%)	0(0.0%)	0(0.0%)
Periorbital edema	8(10%)	8	0(0.0%)
Rash	0(0.0%)	0(0.0%)	0(0.0%)
Fatigue	8(10%)	8(10%)	0(0.0%)
Weight gain	4(5%)	4(5%)	0(0.0%)
Leukopenia	4(5%)	4(5%)	0(0.0%)
Anemia	6(7.5%)	6(7.5%)	0(0.0%)
Thrombocytopenia	6(7.5%)	5(6.25%)	1(1.25%)

Table. 3
Results of Levels of molecular response to Imatinib treatment in 79 patients with CML.

BCR/ABL (IS%)		10–100%	<10%	<1	<0.1	0.00	Total Total number
Molecular response:							
Inadequate response or intolerance* to Imatinib	**Number Patients**	2	8	2	0	2*	14
	Percent patients	(14.3%)	(57.1%)	(14.3%)	(0.0%)	(14.3%)	(100.0%)
Adequate response based on the time of starting treatment	**Number Patients**	0	2	3	2	58	65
	Percent patients	0.0%	3.1%	4.6%	3.1%	89.2%	100.0%
Total	**Number**	2	10	5	2	60	79
	Percent	2.5%	12.7%	6.3%	2.5%	75.9%	100.0%

due to weakness, malaise, and severe bone pain. Initial examinations confirm anemia and Hughes splenomegaly. Bone marrow aspiration is performed for the patient and acute myeloid leukemia is confirmed. Chemotherapy is started for the patient. Eventually the patient dies due to lack of response to treatment and persistence of fever and neutropenia. Due to the poor financial situation of the patient's family; it was not possible to check for T (9; 22) and another chromosomal disorder. Out of the 14 cases, one patient underwent stem cell transplantation during follow-up period of Nilotinib after entering the accelerated phase (the patient is still alive). During the follow-up period of 79 patients, four cases (5.06%) progressed to accelerated/blastic phases. Three patients experienced Blast Crisis and two of them used Imatinib and one case received Nilotinib. Statistically, there was not any significant difference between prescribed medicine and progressive AP/BC ($P = 1$. Fisher's exact test*). There was one case of accelerated crisis and three patients died (one due CVA and two due AML). The second patient with acute myeloid leukemia died during chemotherapy-induced neutropenia.

3.2. Sokal score

Forty patients (50.6%) obtained low sokal score, 31 (39.2%) cases obtained intermediate sokal score and eight (10.1%) obtained high sokal scores. Table 4 shows the relationship between sokal score and therapy line. Out of 14 patients who used Nilotinib, four (28.6%) and three (21.4%) cases obtained sokal scores with low and high score risks respectively. In addition, among 65 cases who used Imatinib, 36 (55.4%) and five (7.7%) patients experienced low and high risk scores respectively. Nevertheless, the number of patients was numerically different in favor of Sokal score with low risk; although, this difference was not statistically significant ($P = 0.1$). In addition, the association between sokal score and medicine switch was examined. Out of eight patients with high sokal scores, five patients (62.5%) were using Imatinib and medication for three patients (37.5%) was changed. In the group with intermediate risk, seven patients (22.6%) had medicine change and 24 patients (77.4%) are still receiving Imatinib. In the group of low risk score, four cases (10%) had medicine change while 36 patients (90%) are still receiving Imatinib. Accordingly, 21.4%, 50% and 28.6% of patients who experienced medicine switch were assigned to high-risk score, intermediate-risk score, and low-risk score groups respectively. There was not any significant relationship between medicine type or medicine change and risk level (>0.05). The relationship between size of spleen and two accelerated and blastic phases was evaluated. Both of the patients with mild size spleen experienced blast crisis; and out of two patients with severe size of spleen, one patient developed blast phase and one case experienced accelerated phase. The patients were tested in terms of the side effects of treatment and the only considerable side effect was periorbital edema in patients who received three tablets and then four tablets daily. Cumulative survival in total number of patients was 91.6% up to the end of study (Fig. 1).

Table 4
The relationship between Sokal score and patients taking imatinib or nilotinib.

Sokal score	Low	Intermediate	High risk	Total
Nolitonib	4	7	3	14
	28.6%	50%	21.4%	100.0%
Imatinib	36	24	5	65
	55.4%	36.9%	7.7%	100.0%
	40	31	8	79
	50.6%	39.2%	10.1%	100.0%

4. Discussion

According to the guidelines, it is important to test molecular response (MR) at the 3rd, 6th, and 12th months after starting treatment with TKIs. The MR is a significant factor for evaluating disease outcome and making decision on medical switch. However, the disease may develop and enter other phases in some of CML patients so that delayed therapeutic decision-making is not desirable. In this research, only a small percent of patients (seven patients) afforded MR after three, six, and 12 months of treatment. The rest of cases ($n = 72$) were tested within different time intervals after treatment and diagnosis and MR evaluation was done after entering into the research plan. In the case of low responses based on the guideline, three options of medicine switch, dose increase, and stem cell transplant would be considered, and the first one was chosen in this study. With mean follow-up equal to 69.67 ± 60, MR of 84.7% of patients was at range of <1 to 0.00. Moreover, molecular response of DMR was achieved with about 75.9% of patients at this follow-up period. It seems that with a longer mean follow-up, deeper responses can be found. Overall, (cumulative) survival of patients was 91.6% at the end of study, which is a significant rate in line with other similar studies. Follow-up of patients with switched medicine was inadequate so that treatment response evaluation was not possible. The sokal scores of patients were evaluated. Although, there was a higher percent of patients in low-risk group than intermediate and high-risk group, this was not statistically a significant difference owing to few numbers of patients. Moreover, the patients who had to receive the switched medicine were at the group with intermediate to high-risk score compared to low-risk sokal score group, which was not also statistically a significant difference. The mean age of the patients in this paper was 41 years that was not consistent with similar studies in this field. However, mean age varies in the developed and developing countries [4]. Another interesting point in 18-year follow-up of our patients was DMR, of which the effect was maintained within a long-term follow-up. The long-term use of medicine is important as the drug withdrawal may lead to disappearance of such therapeutic response in many patients. However, stable and persistent deep responses may require long-term therapies. Nevertheless, Saussele S et al. [21] and Etienne G et al. [22] recommended TKI discontinuation in patients with a sustained DMR for a long time. The side effects of the medicine are highly important factors in long-term use and selecting the treatment type. Drug toxicity of Imatinib was mild in most cases and potentially reversible. Only a few side effects, such as skin rash and abnormal live function tests were observed. Periorbital edema was significant in a number of patients; these patients were advised to take the drug at a dose of 400 and 300 mg every other day, and increase the dose after improvement of the complication. In terms of hematological complications, a number of mild cases were seen at the beginning of

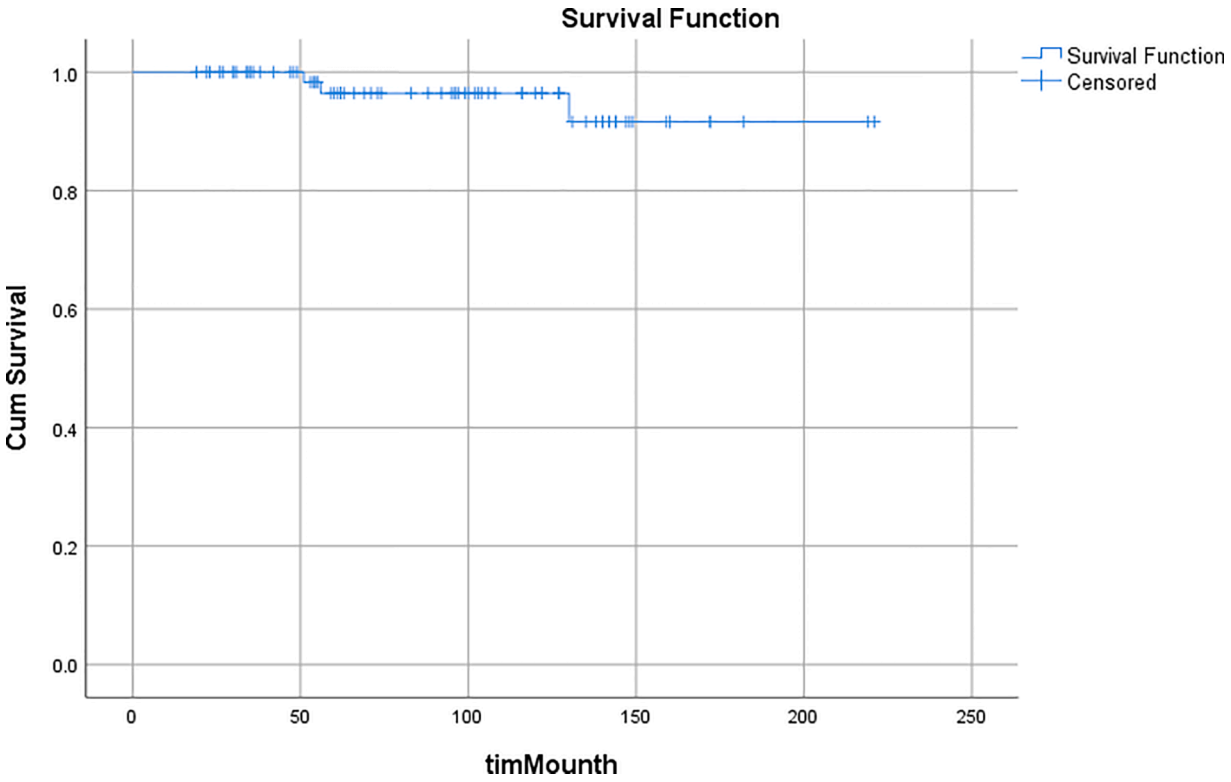

Fig. 1. Cumulative survival in total number of patients.

treatment in the form of leukopenia and thrombocytopenia and improved within a few days with a decrease in drug dose. There was only one case of prolonged thrombocytopenia that did not respond to a dose reduction of Imatinib and the patient's platelets remained in the range of 70,000 – 80,000/ ul. For this patient, like other patients, MR was assessed, which was not in the response range according to the guideline, so the patient was in the group resistant to Imatinib. Therefore, the initial drug was discontinued and Nolitinib was started. After discontinuation of Imatinib, platelets began to increase and remained in the range of 120 to 130 thousand during the follow-up. There are two limitations to our study. First, due to the high cost of molecular tests related to CML in Iran, it is not possible to perform these molecular tests for a large number of patients based on the guideline. Therefore, it has not been possible for the authors to organize data periodically (at different time points) and provide the number of patients who achieved MMR and MMR loss at each time point. Still, the mean follow-up time to medicine change was about 69.67 months. Second, Europin Leukemia Net 2020 has recommendations discontinuing tyrosine kinase inhibitors under special circumstances. Evaluation of the panel (ELN) for discontinuation of Imatinib showed that it requires accurate and expensive laboratory tests, which was not possible for our patients, so that we are currently considering the option of continuing treatment in patients [23]. In this research, Imatinib therapy was well tolerated without showing any late side effects and its side effects were easily handled. Patients treated with nilotinib did not report significant side effects. A 65-year-old patient suffered a cerebral- Vascular Occlusive Event during treatment with Nolitinib. Was Nolitinib effective in this regard? It is not easy to answer for us. A small number of patients reported mild nausea that did not require treatment.This study indicated that Imatinib is still acceptable TKIs for CML. An important point is that molecular test of treatment response evaluation was not done routinely in about 91% of patients; however, the statistics of blastic, accelerated, and death cases were similar to previous studies. The unanswered question of this study is about the effect of routine molecular response test on the disease process.

5. Conclusion

Owing to the safety of Imatinib in a long-term follow-up and its perfect effect on deep molecular response, this medicine is still the first choice for CML patients. Response evaluation was done using molecular method and it was found that Imatinib led to long-term overall survival of the studied patients.

Declaration of Competing Interest

The authors do not have any conflicts of interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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