Research Article
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Haematological and cytogenetic changes in CML patients treated with imatinib mesylate in Western Libya

Abstract

Background: Chronic myeloid leukemia (CML) is a clonal myeloid proliferative disorder of primitive haemopoietic progenitor cells. The incidence of CML ranges between 10 and 15 cases/10^6 /year without any major geographic or ethnic differences. Imatinib mesylate provides good results in the treatment of CML. Early studies demonstrated that Imatinib mesylate can produce clear hematologic and cytogenetic response when used as a treatment of CML patients with positive *BCR-ABL* gene. Nevertheless, some patient with different stages of CML (chronic, accelerated, or acute phases) either relapse or stay unchanged for a long time after initial doses of treatment. This phenomenon led to the fact that we must explore the possible changes expected to appear if we make some changes in the treatment strategy.

Objectives: The present study aimed to evaluate hematologic and molecular responses of CML patients to Imatinib mesylate treatment.

Methods: Eighteen CML patients in chronic phase aged (24–65 years) males and females were treated with Imatinib mesylate (400, 500 or 600 mg/day) for sixteen months. Hematologic and cytogenetic changes were analyzed periodically. **Results:** Overall 18 cases, hematologic response of 14 cases was complete white blood cells (WBCs) decrease to normal range within 4 months) with *P* value of less than *0.0001* whereas in 4 cases WBCs were decreased slowly (after 8 months). A major cytogenetic response was noticed in 4 cases while in others the response was partially or in minor range. The major hematologic and cytogenetic response was noticed when using 600mg/day of Imatinib mesylate. The correlation appeared as a significant positive correlation between the treatment doses and Hb, hematocrit, MCV, MCH, esinophils%, and monocytes %. And a significant negative correlation between the treatment doses and RDW %, platelets count, WBCs count, and basophils %. On the other hand, no correlation between the treatment doses and RBCs Count, MCHC, Neutrophil % and *BCR/APL* ratio %

Conclusion: It can be concluded that treatment of CML patients with Imatinib mesylate caused complete WBCs decrease to normal range. The major hematologic and cytogenetic response was noticed when using a higher dose of Imatinib mesylate.

Keywords: cytogenetic response, hematologic response, imatinib mesylate, Western Libya, clonal myeloid, benzene, translocation, preservatives, obesity, weight gain, thrombocytopenia, granulocytes, oncoprotein

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Abbreviations: CML, chronic myeloid leukemia; WHO, world health organization; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PCR, Polymerase chain reaction; RDW, Red blood cell distribution width

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloid proliferative disorder of primitive haemopoietic progenitor cells. The cytogenetic hallmark of CML is the Philadelphia chromosome, created by a reciprocal translocation between chromosomes 9&22 (t[9;22] [q34;q11]).[1,2] The male is affected more than the female and chronic phase of CML was common in the younger age group.[3] The incidence of CML ranges between 10 and 15 cases/10^6 /year without any major geographic or ethnic differences.[4,5] In spite of leukemia induced factors, there are risk factors that enhance the CML and these factors include lower socioeconomic status, occupational exposure to benzene, formaldehyde, high doses of ionizing radiation among the atomic bomb survivors, other risk factor such as alcohol abuse, obesity, weight gain during adulthood and effects of preservatives or pesticides used in the food industry causes CML.[3,6,7] Clinically in 50% of cases patients with CML are asymptomatic and remaining were present with anemia, splenomegaly, fever, bleeding tendency, hepatomegaly, lymphadenopathy and complications such as renal failure, hearing loss and priapism, and laboratory findings include complete blood count, peripheral blood and bone marrow examinations showing low hemoglobin, total WBC count between 287×10^9/L and 535.7×10^9/L,

thrombocytopenia or normal platelet count or thrombocytosis and peripheral blood smear showing increase number of mature and immature granulocytes including predominantly.[3,8,9]

This altered stem cell proliferates and generates a population of differentiated cells that gradually displaces normal hemopoiesis and leads to greatly expanded total myeloid mass. One important landmark in the study of CML was the discovery of the Philadelphia (Ph) chromosome in 1960; another was the characterization in the1980s of the BCR– ABL chimeric gene and associated oncoprotein and a third was the demonstration that introducing the BCR–ABL gene into murine stem cells in experimental animals caused a disease simulating human CML.[10,11] According to the world health organization (WHO) regardless of the rare CML cases who are not expressing this gene, most of them are *BCR-ABL* positive.[12] Production of this translocation, the *BCR-ABL* tyrosine kinase (a *BCR-ABL* fusion gene) is the molecular target of a recently approved drug, Imatinib mesylate.[13] Imatinib mesylate is the most prominent example of a new generation of anticancer drugs.[14] It is used in treating CML by inducing apoptosis and inhibiting cell proliferation. Although various studies have been conducted on hematologic, cytogenetic, and molecular responses of patients to Imatinib mesylate, only a few studies are available on the efficacy of Imatib.

Determining the patient's response to therapy helps to evaluate the course of therapy and makes it possible to be a few steps ahead in case of any complication. It has been known that some CML patients are resistant to Imatinib and not knowing that may result in disease progression to the next stage. In such cases, management is more complex and sometimes impossible,[15] it is presently the first line treatment of newly diagnosed CML in chronic phase, accelerated phase disease, and even in blast crisis. Advances in translational research leading to better the drug development have seen the emergence of second-generation tyrosine kinase inhibitors and Src kinase inhibitors leading to successful treatment of Imatinib resistant cases. With these developments, CML is becoming a chronic disease such as diabetes and hypertension.[16] Imatinib mesylate provides good results in the treatment of CML in general.[17] Imatinib mesylate, a selective inhibitor of *BCR-ABL* kinase activity, selectively inhibits downstream signaling and the growth of BCR-ABL+ cells, inducing apoptosis of these cells.[2,18]

The development of the *BCR-ABL*-targeted Imatinib mesylate represents a paradigm shift in the treatment of CML. Data indicate that the level of immune responses against CML is low before Imatinib, rises as treatment is administered and declines again when the *BCR-ABL* transcript numbers fall too low levels.[2,19] Imatinib causes persisting but mostly mild to moderate side-effects with significant impact on the quality of life including fatigue, weight gain, peripheral and periorbital edema, bone and muscle aches, nausea and others.[5]

Objectives

Early studies demonstrated that Imatinib mesylate can produce clear hematologic and cytogenetic response when used as a treatment of CML patients with positive *BCR-ABL* gene. Nevertheless, some patient with different stages of CML (chronic, accelerated, or acute phases) either relapse or stay unchanged for a long time after initial doses of treatment. This phenomenon led to the fact that we must explore the possible changes expected to appear if we make some changes in the treatment strategy. So, the present study aimed to evaluate hematologic and molecular responses of CML patients to Imatinib mesylate treatment.

Materials and methods

Eighteen CML patients in chronic phase (7males& 11females) aged (24–65years) were treated with Imatinib mesylate (400, 500 or 600mg/day) for sixteen months at standard dosage were enrolled in this prospective study. All patients were seen in the department of hematology at the National Cancer Institute, Sabratha, Libya for sixteen months from January 2017 to April 2018. CML patients at the time of data collection were on average 41.8years old (range 24-65). This study was approved by the Research and Ethical Committee of the National Cancer Institute, Sabratha. Patients satisfying the inclusion criteria were enrolled in the study. Written informed consent was obtained from every patient before Imatinib therapy was started. The patients were followed-up for 16months of treatment. All patients were assessed every month of the treatment and dose of the drug was adjusted every month based on the clinical judgment and lab reports. The recommended dose of Imatinib for the chronic phase is 400mg daily, increased to 600mg daily or 400mg bid. Complete blood count was done after every month of treatment. All patients were shown to be Ph-positive via fluorescence in situ hybridization (FISH) analysis, or p210 *BCR/ABL* transcripts positive via real-time reverse transcriptase polymerase chain reaction (*RT-PCR*) *assay* of peripheral blood samples. FISH analysis for Ph positivity or *RT-PCR* analysis for *BCR/ABL* transcription levels was performed at 4month intervals.

Method for molecular genetic analysis of the BCR-ABL 1 expression

Total RNA was isolated, cDNA conversion was performed and the *BCR-ABL* 1 fusion transcripts b2a2 and b3a2 were amplified using a multiplex real-time PCR assay.[20] ABL1 was used as a house-keeping gene. The standardized definition of deep molecular response is dependent on the level of sensitivity[21]: MR4.0: IS-NCN values≤0.01% with>10,000<32,000 *ABL1* copy numbers

MR4.5: IS-NCN values≤0.0032% with 32,000<100,000 *ABL* 1 copy numbers

MR5.0: IS-NCN values≤0.001 % with≥100,000 *ABL* 1 copy numbers

If an optimal response for survival and deeper, stable, treatment-free remission is defined by *BCR-ABL*1/*ABL* 1 transcript level≤10% at three months,≤1 % at six months, S 0.1% (MMR) at one year and ≤0.01% (MR4) later on.[22] When MR4 is achieved; the European Leukemia Network (ELN) recommends PCR of *BCR-ABL* 1 transcripts every 6-12 months.[23]

Statistical analysis

The data were analyzed using Graph Pad Prism software version 5. The statistical significance of differences between groups was evaluated with the Kruskal-Wallis one-way analysis of variance. Correlations between the treatment doses and variation in haematological parameters and PCR results were evaluated with the Pearson test. *P*-value of *<0.05* was used to establish statistical significance.

Results

Eighteen CML patients in chronic phase, 7 males (39%) & 11 females (61%) (Figure 1), mean age 41.8 years (24–55 years), (Figure 2) shows the distribution of CML patients according to age groups. In male patients, 43% were in (30-39), 29% were in (50-59), 14%

in (20-29), and (40-49) years but in female patients, 55% were in (40–49), 18% in (30-39), 9% in (20-29), (50-59), and (60-69) years. Overall 18 cases, the hematologic response of 14 cases was complete WBCs decrease to normal range within 4 months) with *P* value of less than 0.0001 whereas in 4 cases WBCs were decreased slowly (after 8months). The major hematologic and cytogenetic response was noticed when using 600mg/day of Imatinib mesylate. The data present in the Table 1 and demonstrated by (Figures 3–15) shows the effect of treatment of CML patients with Imatinib mesylate on haematological parameters and PCR results.

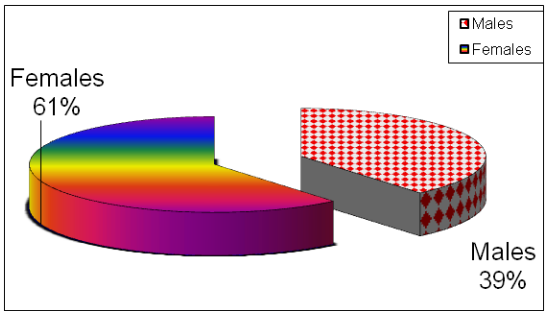

Figure 1 Distribution of CML patient according to gender.

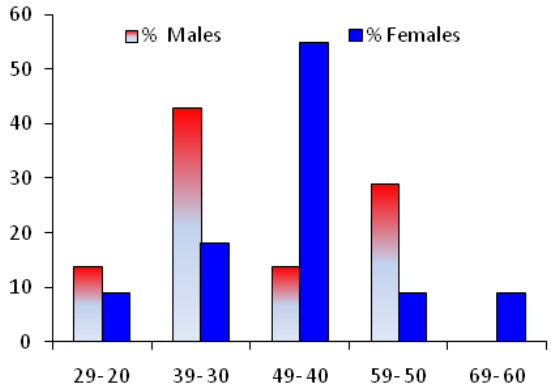

Figure 2 Distribution of males and females CML patient according to age groups.

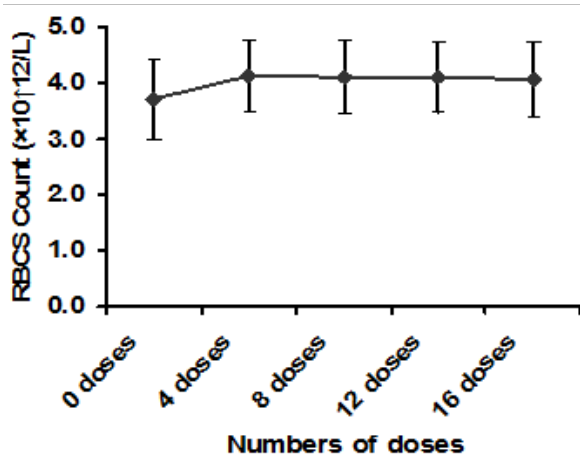

Figure 3 Effect of treatment of CML patients with Imatinib mesylate on RBCs count.

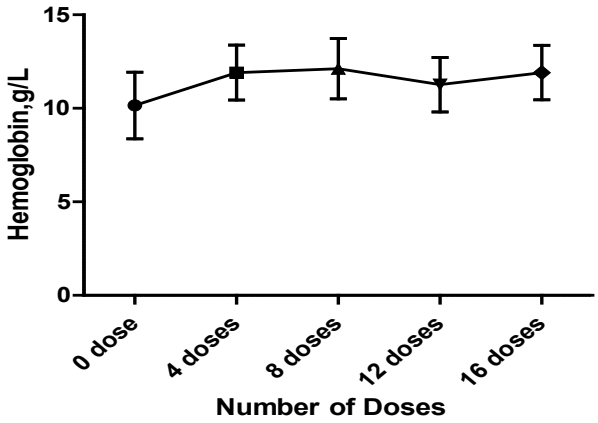

Figure 5 Effect of treatment of CML patients with Imatinib mesylate on hematocrit value.

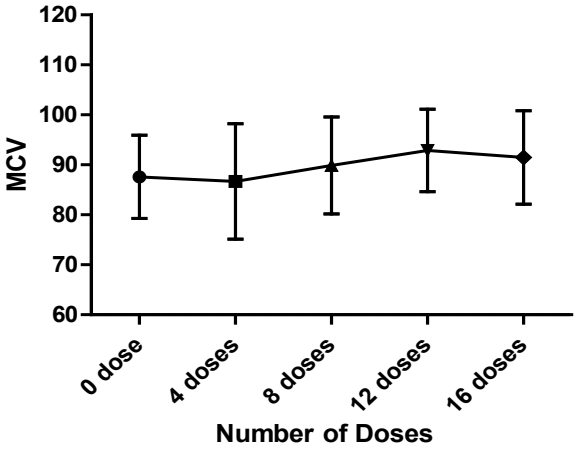

Figure 6 Effect of treatment of CML patients with Imatinib mesylate on MCV.

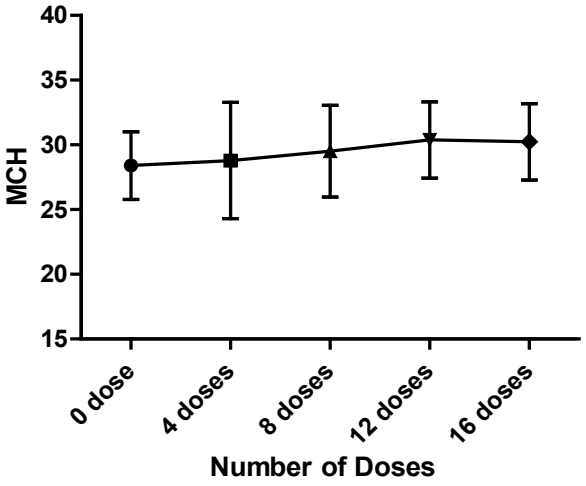

Figure 7 Effect of treatment of CML patients with Imatinib mesylate on MCH.

Citation: Jbireal JM, Azab AE, Alzahani S, et al. Haematological and cytogenetic changes in CML patients treated with imatinib mesylate in Western Libya. *Hematol Transfus Int J.* 2019;7(3):50–57. DOI: 10.15406/htij.2019.07.00205

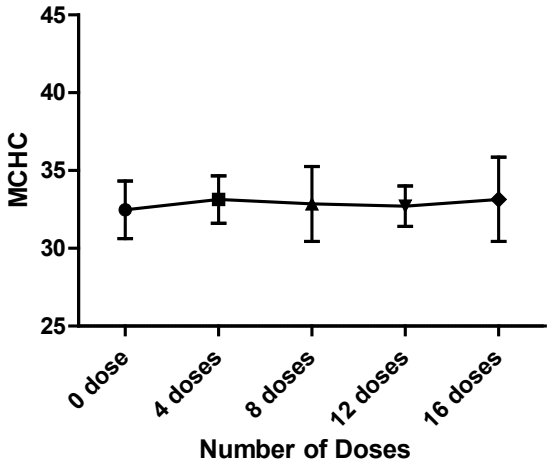

Figure 8 Effect of treatment of CML patients with Imatinib mesylate on MCHC.

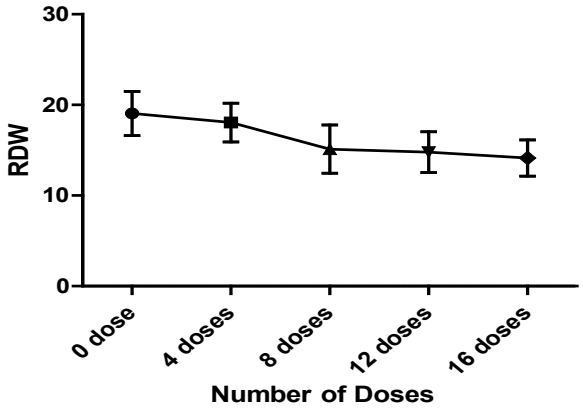

Figure 9 Effect of treatment of CML patients with Imatinib mesylate on RDW.

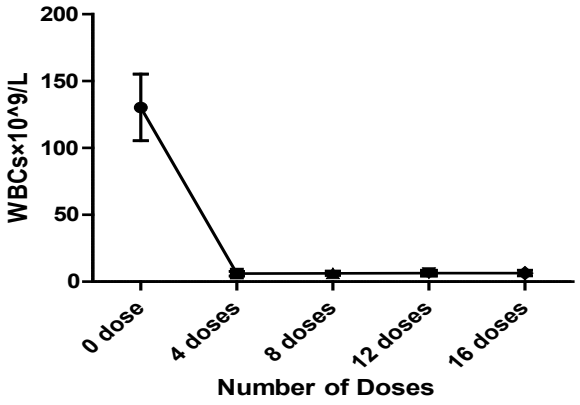

Figure 10 Effect of treatment of CML patients with Imatinib mesylate on WBCs count.

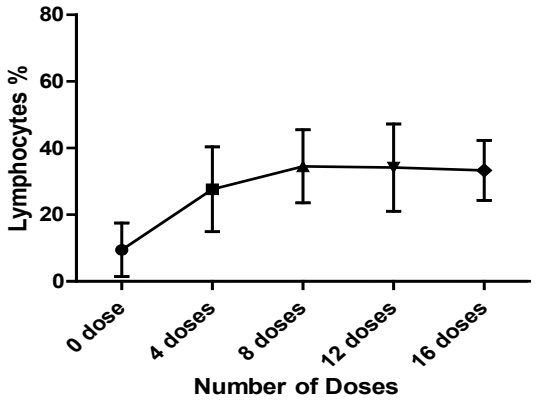

Figure 11 Effect of treatment of CML patients with Imatinib mesylate on lymphocytes %.

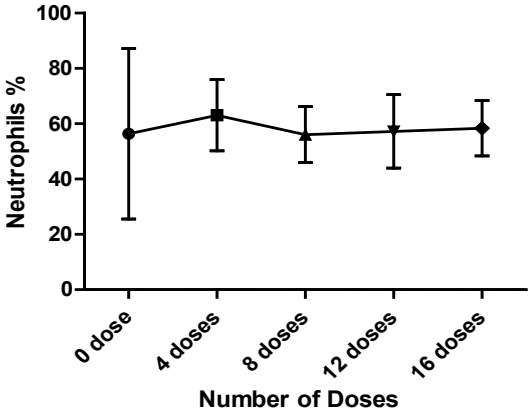

Figure 12 Effect of treatment of CML patients with Imatinib mesylate on neutrophil %.

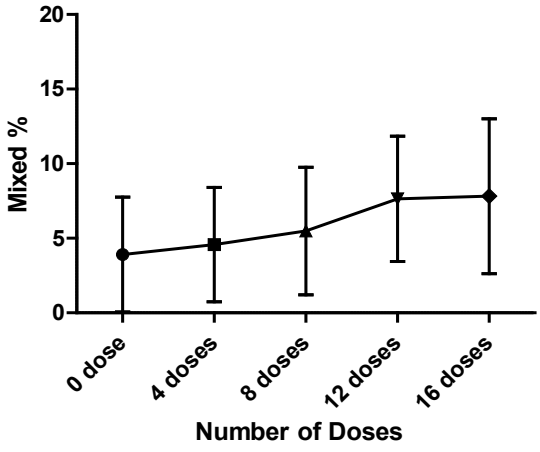

Figure 13 Effect of treatment of CML patients with Imatinib mesylate on mixed %.

Citation: Jbireal JM, Azab AE, Alzahani S, et al. Haematological and cytogenetic changes in CML patients treated with imatinib mesylate in Western Libya. *Hematol Transfus Int J.* 2019;7(3):50–57. DOI: 10.15406/htij.2019.07.00205

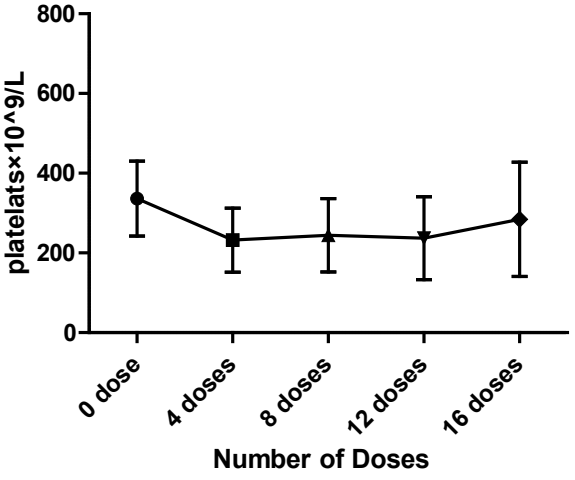

Figure 14 Effect of treatment of CML patients with Imatinib mesylate on blood platelets count.

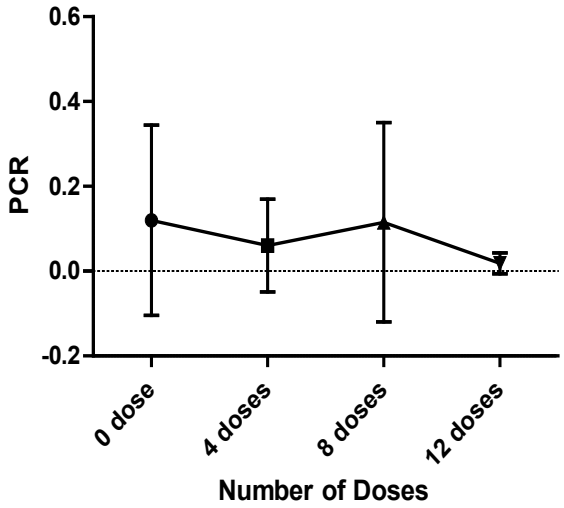

Figure 15 Effect of treatment of CML patients with Imatinib mesylate on BCR/APL ratio (%).

Table 1 Effects of treatment of CML patients with Imatinib mesylate on haematological parameters and PCR results

Number of doses	Number of doses						
							P value
	0 dose	4 doses	8 doses	12 doses	16 doses		
						P Value	summary
Parameters	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD		
RBCs Count (x1012/L)	3.71±0.72	4.12±0.64	4.10±0.66	4.11±0.63	4.07±0.67	0.351	ns
Hb (g/dl)	10.16±1.78	11.91±1.465	12.12±1.612	11.27±1.455	11.91±1.456	0.003	**
Haematocrit %	5.34±31.34	4.69±34.08	4.46±36.35	3.84±36.37	4.83±36.67	0.0187	*
MCV (µ3)	87.60±8.33	86.67±11.55	89.89±9.701	92.86±8.250	91.49±9.357	0.8241	ns
MCH (pg)	2.62±28.40	4.49±28.79	3.54±29.51	2.94±30.38	2.95±30.23	0.4834	ns
MCHC (g/dl)	1.85±32.47	1.53±33.14	2.40±32.85	1.30±32.71	2.71±33.15	0.4435	ns
RDW %	2.44±19.06	2.14±18.06	2.66±15.12	2.24±14.79	2.01±14.13	0.0005	**
Platelets Count x109/L	336.6±94.1	232.0±80.55	244.3±92.00	237.1±104.0	284.4±143.2	0.008	**
WBCs Count x109/L	130.3±24.9	6.04±1.744	6.31±1.587	6.44±1.663	6.47±2.035	0	**
Lymphocytes %	0.15±12.312	12.74±27.63	10.94±34.53	13.10±34.16	8.99±33.31	0.0328	*
Neutrophils%	30.8±56.40	12.88±63.06	1015±56.07	13.28±57.23	9.97±58.38	0.8572	ns
Mix%	0.3±3.919	3.83±4.58	4.28±5.49	4.20±7.64	5.20±7.82	0.3031	ns
BCR/APL ratio (%)	0.120±0.23	0.060±0.109	0.115±0.235	0.018±0.025	--	0.6988	ns

(ns): non-significant difference compared to 0 dose group ($P \geq 0.05$). (*): significant difference compared to 0 dose group ($P<0.05$). (**): highly significant difference compared to dose group ($P<0.01$).

Treatment of CML patients with Imatinib mesylate caused a non significant (P=0.351) increases in RBCs count after 4,8,12, and 16 doses post-treatment (4.12 $x10^{12}$/L, 4.10$x10^{12}$/L, 4.11$x10^{12}$/L, and 4.07$x10^{12}$/L), respectively as compared to untreated patients (0 dose group) (3.71$x10^{12}$/L) (Table1) (Figure 3). Hemoglobin concentration was increased significantly (P=0.0030) in patients treated with Imatinib mesylate after 4 doses (11.91g/dl), 8 doses (12.12g/dl), 12 doses (11.27g/dl), and 16 doses (11.91g/dl) post-treatment, when compared with untreated patients (0 dose group) (10.16g/dl), as shown in Table 1 and (Figure 4).

The data shown in (Table 1) (Figure 5) indicated a significant (P=0.0187) increase of hematocrit value 34.08, 36.35, 36.37, and 36.67% after 4, 8, 12, and 16 doses of treatment of patients with Imatinib mesylate, respectively as compared with untreated patients (0 dose group) (31.34 %). The MCV value, MCH, and MCHC levels

were showed a non-significant changes (*P*=0.8241, *P*=0.4834, and *P*=0.4435) subsequent to 4, 8, 12, and 16 doses of Imatinib mesylate treatment (Table 1) (Figure 6–8).

On the other hand, treatment of patients with Imatinib mesylate induced a significant (*P*=0.0005) decrease in RDW % after 4, 8, 12, and 16 doses of treatment 18.06, 15.12, 14.79, and 14.13 %, respectively as compared with untreated patients (0 dose group) (19.06 %) (Table 1) (Figure 9) The effects of treatment of patients with Imatinib mesylate on blood platelets count are presented in table (1) and figure (10). Blood platelets count decreased significantly (*P*=0.008) 4,8,12, and 16 doses post–treatment, (232 $x10^9$/L, 244.3 $x10^9$/L, 237.1 $x10^9$/L, and 284.4 $x10^9$/L), respectively as compared to the untreated patients (0 dose group) (336.6 $x10^9$/L).

The data recorded in (Table 1) (Figure 11) indicated a significant (*P= 0.000*) decrease in WBCs count in patients treated with Imatinib mesylate after 4 doses (6.04 $x10^9$/L), 8 doses (6.31 $x10^9$/L), 12 doses (6.44 $x10^9$/L), and 16 doses (6.47 $x10^9$/L) compared to the untreated patients (0 dose group) (130.3 $x10^9$/L). Overall 18 cases, the hematologic response of 14 cases was complete WBCs decrease to normal range within 4 months) with *P* value of less than 0.0001 whereas in 4 cases WBCs were decreased slowly (after 8months*)*. On the other hand, lymphocytes % was significantly (*P*=0.0328) increased after 4,8,12, and 16 doses of treatment of patients with Imatinib mesylate 27.63, 34.53, 34.16, and 33.3 %, respectively as compared with untreated patients (0 dose group) (12.31%) (Table 1) (Figure 12)

Unaltered neutrophil % and Mix % were observed in CML patients after treatment with Imatinib mesylate; after 4,8,12, doses, and 16 doses, compared with the untreated patients (0 dose groups). These data are presented in (Table 1) (Figure 13,14) A major cytogenetic response was noticed in 4 cases while in others the response was partially or in minor range. *BCR/APL* ratio (%) was a non significantly changes after 4, 8, 12, and 16 doses of Imatinib mesylate treatment as compared to the untreated patients (0 dose group) (Table 1) (Figure 15)

The data in (Table 2) show the correlation between the treatment doses & variation in haematological parameters and PCR results. This correlation appeared as a significant positive correlation between the treatment doses and Hb, hematocrit, MCV, MCH, Esinophils%, and Monocytes % and a significant negative correlation between the treatment doses and RDW%, Platelets Count, WBCs count, and Basophils %. On the other hand, no correlation between the treatment doses and RBCs Count, MCHC, Neutrophils %, and *BCR/APL* ratio %

Table 2 Correlation between the treatment doses & variation in haematological parameters and PCR results

Parameters	Spearman r	P value (two-tailed)	P value summary
RBCs Count	0.1527	0.1735	ns
Hemoglobin	0.3317	0.0025	**
HCT	0.3568	0.0011	**
MCV	0.2682	0.0155	*
MCH	0.2719	0.0141	*
MCHC	-0.03032	0.7882	ns
RDW %	-0.6147	< 0.0001	***
Platelets Count	-0.3098	0.0049	**
WBCs Count	-0.5462	< 0.0001	***
Neutrophils%	-0.1296	0.2885	ns
Esinophils%	0.7669	0.0008	***
Basophils %	-0.5329	0.0408	*
Monocytes %	0.7909	< 0.0001	***
BCR/APL ratio (%)	-0.1108	0.6326	ns

(*) significant correlation at (*P*<0.05), (**) significant correlation at (*P*<0.01), (***)significant correlation at (*P*<0.001).

Discussion

Imatinib mesylate, the first molecularly targeted therapy for CML, produces a rapid and dramatic resolution of the peripheral blood abnormalities associated with CML. The hematologic responses have been reported to occur typically within 2 weeks after initiation of Imatinib mesylate treatment, with complete hematologic responses by 4 weeks,[24, 25] In the current study, treatment of CML patients with Imatinib mesylate caused non-significant changes in RBCs count, MCV value, MCH, and MCHC levels, a significant increase in hemoglobin concentration, hematocrit value, and lymphocytes % as compared with untreated patients. On the other hand, a significant decrease in RDW %, WBCs and Blood platelets count as compared with untreated patients. But, neutrophil % and Mix % were unaltered compared with untreated patients**.** Our results are in agreement with the results of *Jain et al.*[26], who reported that after 12months of treatment with Imatinib, 95% of patients achieved complete hematological response in Imatinib treated patients when compared with untreated patients. WBC count analysis showed a significantly better profile (*P<0.0001*) in the Imatinib group. Also, in the study done by *Druker et al.*[24], *Kantarjian et al.*[27], and *O'Brien et al.*[28], around 95% of the patients had achieved a complete hematological response. *Braziel*

et al.[25], reported that patients treated with Imatinib mesylate at an effective oral dose (300 to 600mg/day) were followed with peripheral blood counts, marrow examination, and cytogenetic studies at 0, 2, 5, 8, 11, and 14months. By 2 months, 17 of 18 patients achieved complete hematologic responses; 1 reached complete hematologic responses by 5 months, and 1 at 11 months.

Five of 18 patients developed cytopenias requiring treatment interruption and/or dose reduction, but all were able to continue incomplete hematologic responses on the study. Also, the study of *Oyekunle et al*.,[29], showed that the clinical phase of the disease at diagnosis and the hematocrit can be used to stratify patients into low, intermediate, and high risk groups, with significantly different survival outcomes in Nigerian patients with CML. *Aissata et al.,*[17], reported that CML patients were severely symptomatic with a performance status ≥2 in 100%, splenomegaly in 100%, fever in 74%, hepatomegaly in 48%, bone pains in 48% and lymphadenopathy in 22%. Splenomegaly was relatively large, ≥10cm in 74%, probably due to the long period of consultation.

Bileni and Erdem et al.,[30] reported that at the end of the second month of treatment of chronic-phase CML patients with Imatinib therapy in the hematology unit of Ataturk University Medical Faculty Training Hospital, all of the patients had achieved complete hematologic response. After 12months, the rate of complete cytogenetic response was 71%. The exact mechanism by which anemia can impact on the overall survival of patients with CML remains unclear; however, well known that in several lympho proliferative disorders, such as chronic lymphocytic leukemia and myelomas, anemia is recognized as a poor prognostic factor, though this has never been established for CML. In these conditions, anemia is typically an indication of the extent of marrow infiltration by the malignant cells and consequently a surrogate of tumor bulk. Similarly, in this case, it may also be a reflection of advanced disease, which is yet to meet the definition of disease progression. It may also be a reflection of how patients' pre-morbid state may affect disease outcome, as many of these patients may have been anemic long before CML was diagnosed.[29]

In the present study, the correlation between the treatment doses and variation in haematological parameters and PCR results were appeared as a significant positive correlation between the treatment doses and Hb, hematocrit, MCV, MCH, esinophils%, and monocytes %, and a significant negative correlation between the treatment doses and RDW %, Platelets

Count, WBCs count, and Basophils%, but no correlation between the treatment doses and RBCs Count, MCHC, Neutrophils % and *BCR/APL* ratio %

On the other hand, Abdalruhman[11], reported that absolute lymphocyte count inversely correlated with the duration of treatment, but there is no statistically significant reduction of absolute lymphocyte count, that is similar to the data of *Santachiara et al.,*[31]About the hematological indices; MCV and MCH are inversely correlated with duration of treatment with a picture of hypochromic microcytic red cells may be due to chronic illness.

Imatinib has unequivocally established the value of molecularly targeted treatment in cancer medicine in general and, of course, specifically in CML and related diseases. It has also provided further evidence that the *BCR-ABL* gene must be the initiating event for chronic phase CML. Remarkably, this gene continues to play a pivotal role even when patients in chronic phase CML develop resistance to Imatinib and mutant forms of the gene are identified. The T315I mutant appears to be resistant not only to escalating doses of Imatinib, but also to the second generation TKIs, nilotinib and dasatinib.[32] In the present study, a major cytogenetic response was noticed in 4 cases while in others the response was partially or in minor range. *BCR/APL* ratio (%) was a non-significantly changes after Imatinib mesylate treatment as compared to the untreated patients.

Our results are similar to the result of Abdalruhman[11], who reported that Imatinib mesylate can induce a complete cytogenetic response in a high percent of CML patients. Cytogenetic response correlates well with the duration of treatment. Twenty four out of thirty one CML patients treated with the Imatinib regimen reached a complete cytogenetic response, four patients reached a major cytogenetic response and only three did not reach a partial cytogenetic response similar to the result of *Santachiara et al.,*[31] Also, *Razmkhah et al.,*[15], reported that molecular and hematologic responses to Imatib were acceptably good. Ninety percent of the patients showed some sort of hematologic response that had no significant correlation with a patient's age or sex, dosage, or duration of Imatib consumption. Overall, 46.7% of patients showed a complete molecular response, 43.3% showed a partial molecular response, and 10% showed no molecular response to Imatib. A reverse significant (P=0.05) correlation was noted between the type of molecular response and the patient's age. Possible mechanisms of resistance to imatinib mesylate are largely unknown. Preliminary data in cell lines and in patients with advanced-stage CML have suggested that the resistance to imatinib mesylate may be mediated by *BCR-ABL* gene amplification or point mutations of the *BCR-ABL* kinase, with reactivation of kinase activity.[25,33–35]

Conclusion

It can be concluded that treatment of CML patients with Imatinib mesylate caused complete WBCs decrease to normal range.

The major hematologic and cytogenetic response was noticed when using a higher dose of Imatinib mesylate.

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None

Conflicts of interest

The author declares that there are no conflicts of interest.

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