Boffin Access

Open Access Journal | Volume: 1.2

International Journal of Biopharmaceutical Sciences

ISSN 2517-7338

Chronic Myeloid Leukemia in South Yemen

Abdul-Rahman SA[1]
Hamid GA[1*]
Nasher S[2]
Hadi YA[3]

[1]Faculty of Medicine, Aden University, Aden, Yemen
[2]Faculty of Medicine, Taiz University, Taiz, Yemen
[3]National Oncology Center, Sana'a, Yemen

Abstract

Objectives: There is no any published chronic myeloid leukemia epidemiology and evaluation of the hematological and molecular response of chronic myeloid leukemia patients.

Material and Methods: This is a descriptive study conducted at National Oncology Center-Aden, South Yemen from September 2014-March 2016.

Results: 50 patients were studied, 22 of them were males and 28 were females, the age is ranged between 20-71 years old with a mean age 41.9 years. The most common complaint was fatigability 86%, followed by fever and abdominal distension 78%, 76% respectively while in 82% of patients splenomegaly was the prominent sign detected during the examination. Most patients were anemic at diagnosis with a mean hemoglobin 10.2 g/dl, leukocytosis was observed in 90% of patients ranging from 4.6×10^9 up to 290×10^9 with a mean WBC count about 40.0×10^9. The dramatic hematological improvement was observed with the achievement of CHR in 84% of patients which considered as an optimal response.

Monitoring early molecular response after three months of starting imatinib revealed an achievement of optimal response in 60% of patients (≥ 1 log reduction of standardized baseline value which is 72.2% in our study), suboptimal or warning response is observed in 22%, (<1 log reduction but >standardized baseline value), and failure to response in 18% (6% didn't show any molecular response but still in chronic phase, 8% progress to blast crisis, 4% drug intolerance).

Conclusions: 1) Chronic myeloid leukemia found to be more common in patients within 4^{th}-5^{th} decades in our study, with slight female predominance (0.8:1 M:F ratio). 2) Early molecular response is significant and optimal early molecular response was achieved by 60% of patients, 22% showed a suboptimal response while only 18% failed to show any molecular response.

Keywords

Epidemiology; Chronic myeloid leukemia (CML); BCR-ABL; Tyrosine Kinase Inhibitor; Aden; Yemen

Introduction

Chronic myeloid leukemia (CML) is a hematopoietic disorder characterized by the malignant expansion of bone marrow stem cells, with the presence of a reciprocal translocation between chromosomes 9 and 22 resulting in the fusion gene, BCR-ABL, whose product is a 210-kd protein with tyrosine kinase activity [1]. The disease has an incidence of 1-2 cases per 100,000 adults, and accounts for 15% of newly diagnosed cases of leukemia in adults [2].

Clinically, CML is characterized by left-shifted granulocytosis and splenomegaly that is discovered either incidentally or in association with symptoms from anemia, marked splenomegaly, or high cell turnover [3,4]. Usually, CML starts with a chronic phase (CP-CML) that lasts for an average of 4 years and subsequently progresses to either acute myeloid or lymphoid leukemia [5].

The typical laboratory findings in CML are leukocytosis with a remarkable left shift of the differential count, basophilia, and eosinophilia. Platelet count may be either high or low, and mild anemia is commonly observed. The peripheral blood findings change with disease progression [6]. The bone marrow becoming notoriously hypercellular with marked myeloid hyperplasia and increase in M:E ratio, all stages of myeloid maturation are present, with a predominance of myelocytes [7].

Fortunately, the diagnosis is rarely problematic with the development of modern laboratory diagnostic techniques. It depends on the demonstration of the Philadelphia chromosome by cytogenetic analysis or BCR-ABL gene by reverse-transcriptase polymerase chain reaction or floresence in situ hybridization (FISH) [8].

Article Information

DOI: 10.31021/ijbs.20181110
Article Type: Research Article
Journal Type: Open Access
Volume: 1 **Issue:** 2
Manuscript ID: IJBS-1-110
Publisher: Boffin Access Limited

Received Date: 06 July 2018
Accepted Date: 28 September 2018
Published Date: 29 September 2018

*Corresponding author:

Gamal Abdul Hamid
Faculty of Medicine
Aden University, Yemen
Tel: +967-711323798
E-mail: drgamal2000@yahoo.com

Citation: Hamid GA, Abdul-Rahman SA, Nasher S, Hadi YA. Chronic Myeloid Leukemia in South Yemen. Int J Biopharm Sci. 2018 Sep;1(2):110

For a long time, chronic myeloid leukemia remained a chronic leukemia subtype with little or no response gained. The treatment is dramatically improved during last decade with the development of Tyrosine kinase inhibitors and the introduction of Imatinib into clinical practice in 2001, which considered as golden standard target therapy and the first line drug of choice in chronic phase of chronic myeloid leukemia, later on, Nilotinib, Dasatinib, Bosutinib, and Ponatinib were introduced in clinical practice showing higher potency against BCR-ABL and against imatinib resistance or intolerance [9]. The rapidity of molecular response may also have additional prognostic significance [10].

Many consider the achievement of a major molecular response (MMR) a goal of imatinib and failure to achieve it by 18 months of imatinib treatment may represent a suboptimal or failure response and review of therapy was recommended [11].

The aim of this study is to evaluate the efficacy of Imatinib as first-line treatment in chronic phase chronic myeloid leukemia patients through assessment of hematological and early molecular response and its impact on disease outcome.

Materials and Methods

This is a descriptive study conducted at National Oncology Center-Aden from September 2014-March 2016. The total number of subjects were 50 adult patients, who diagnosed by complete blood count, blood film, bone marrow aspiration and confirmed by molecular detection of BCR-ABL using quantitative real-time PCR.

Inclusion criteria

The study population included adult patients who were positive for BCR-ABL fusion gene chronic myeloid leukemia in chronic phase, either previously or newly diagnosed who were not receiving tyrosine kinase previously.

Exclusion criteria

1. Chronic myeloid leukemia patients in accelerated and blast crisis
2. Chronic myeloid leukemia patients who are negative for the BCR-ABL fusion gene
3. Patient who is previously treated with imatinib or other Tyrosine kinase inhibitors

Data collection

1. Data were collected from patients with chronic myeloid leukemia in chronic phase who are newly diagnosed or those who were previously diagnosed and treated with hydroxyurea after a period of drug tapering then to be followed up during 3 months after introducing imatinib. All patients interviewed were between 20-71 years old, the interview includes detailed medical history, physical examination including liver, spleen and lymph node. Allopurinol was prescribed to all patients with elevated serum uric acid prior to Imatinib.
2. Blood counts obtained at the time of diagnosis then monthly from venous blood, 5 ml was collected from each patient in EDTA tube and sent for complete blood cell count (CBC) by an automated blood counter (Sysmex KX-21N) blood film was performed also.
3. Bone marrow aspiration was performed either from suprasternal or posterior iliac crest, with enough slides for Leishman stain to established the diagnosis morphologically and determine disease phase.
4. A minimum of 5 ml venous blood collected in EDTA tubes, stored at 2-8°C for a maximum of 48 hours before processing is sent for molecular study for BCR-ABL at diagnosis and three months after starting imatinib.

Treatment response either

Hematologic response (HR) is a rough measure based on peripheral blood counts and spleen size. Molecular response (MR) is determined by serial measurements of BCR-ABL transcript level in peripheral blood by qRT-PCR and by calculating log reduction from baseline BCR-ABL ratio which was 72% in our study after converting the ratio to the percentage.

Optimal response: Haematological: Normalization of the peripheral blood count and impalpable spleen one month after starting treatment.

Molecular: BCR-ABL/ABL ratio ≥ 1 log reduction 3 months after starting treatment.

Failure: Haematological: Failure to achieved peripheral blood count normalization one month after treatment.

Molecular response: BCR-ABL<1 log reduction from baseline value 3 months after starting treatment.

Suboptimal response (warning): Zone between optimal and failure.

Statistical analysis

The employed technique of data collection which is an open-close questionnaire needed to accomplished the study.

The collected data was introduced into the SPSS program (version 20), the analysis data tabulated in statistical tables and graphs. Descriptive statistics comprises frequency, mean, median, standard deviation and percentages, while inferential statistics comprises of differences between means of the paired sample (before and after taking imatinib drug) under the significant level of $p \leq 0.05$.

Results

In this study, 50 patients with chronic myeloid leukemias were included. Females were more than males (58.0% *vs.* 42.0%) with no significant difference between them ($p>0.05$). Their age range from 20 to 71 years and the mean age was 41.9 ± 13.5 years.

The peak age for the studied CML patients was the 4th and 5th decades (52.0% for both) (Tables 1 & 2).

The common complaints about the studied patients were fatigue, fever and abdominal distension (86.0%, 78.0% and 76.0% respectively), and the commonly observed signs were splenomegaly and pallor (82.0% and 70.0% respectively) (Table 3).

The studied patients were having baseline mean hemoglobin of 10.2 ± 1.8 g/dl, total WBCs of 65.7 ± 60.2 × 10^9/L, platelets of 448.2 ± 230.7 × 10^9/L and absolute neutrophils count of 29.2 × 10^9/L. In regard to the sex of CML patients, there is a significantly lower mean hemoglobin level among female in compare to male patients (9.5 *vs.* 11.1 g/dl) (Table 4).

In Table 4 when comparing the baseline hematological parameters and after one month of imatinib therapy, there is a significant reduction in the total WBCs count from 65.7 to 9.5 × 10^9/L, significant reduction in ANC from 29.2 to 5.6 × 10^9/L and significant reduction in platelets count from 448.2 to 246.2 × 10^9/L. Hemoglobin concentration showed mild insignificant elevation from 10.2 to 10.3 g/dl.

	Chronic phase CML (n=50)	
	No.	%
Sex		
Malev	21	42.0
Female	29	58.0
Age group (years)		
<30	10	20.0
30-39	13	26.0
40-49	13	26.0
50-59	9	18.0
≥ 60	5	10.0
Mean age ± SD (Min.-Max.)	41.9 ± 13.5 (20-71)	

Table 1: Demographic characteristics of the studied patients with CML

	Male (n=21)		Female (n=29)		Total (n=50)		*p*-value
	No.	%	No.	%	No.	%	
-Symptoms							
Fatigue	18	85.7	25	86.2	43	86.0	0.635
Fever	17	81.0	22	75.9	39	78.0	0.471
Abdominal distension	18	85.7	20	69.0	38	76.0	0.151
Weight loss	12	57.1	12	41.4	24	48.0	0.208
Bone pain	6	28.6	7	24.1	13	26.0	0.486
Signs							
Splenomegaly	21	100.0	20	69.0	41	82.0	**0.004***
Pallor	11	52.4	24	82.8	35	70.0	**0.023***
Recurrent infection	4	19.0	5	17.2	9	18.0	0.577
Hepatomegaly	5	23.8	2	6.9	7	14.0	0.100

**p*-value is statistically insignificant

Table 2: Clinical presentation by sex of the studied patients with CML

Parameter	Male (n=21)	Female (n=29)	Total (n=50)	*p*-value
	Mean ± SD Median (Min.-Max.)	Mean ± SD Median (Min.-Max.)	Mean ± SD Median (Min.-Max.)	
Hemoglobin concentration (g/dl)	11.1 ± 1.7 10.7 (8.3-14.3)	9.5 ± 1.5 9.2 (6.3-12.7)	10.2 ± 1.8 9.9 (6.3-14.3)	**0.002***
Total WBCs count ($X10^9$/L)	74.9 ± 61.9 35.0 (4.6-290)	59.5 ± 58.8 45.0 (5.5-243.0)	65.7 ± 60.2 40.0 (4.6-290.0)	0.870
Platelets count ($X10^9$/L)	419.4 ± 226.6 371.0 (54.0-825.0)	469.1 ± 235.3 457.0 (141-1090)	448.2 ± 230.7 445.0 (54.0-1090)	0.457

**p*-value is statistically insignificant

Table 3: Baseline hematological findings by sex of the studied patients with chronic myeloid leukemia

The differential WBCs count after one month of imatinib therapy showed a significant elevation in the percentage of lymphocytes from 10.7 to 33.8% and a significant reduction in the percentage of myelocytes from 18.1 to 5.0%, metamyelocytes from 8.6 to 5.4% and the band form from 11.3% to 7.2% (Table 5).

The BCR-Abl/Abl ratio at diagnosis of the studied patients with chronic CML was ranging from 0 to 23.0% with a mean of 2.88 ± 4.45%. This mean was not significantly differing between both sexes (p=0.932) (Table 6).

Evaluation of early molecular response in the studied patients with chronic phase chronic myeloid leukemia revealed that 26.0% of them had an optimal early molecular response after three months of starting Imatinib. These patients showed ≥ 1 log reduction but <3 log reduction of standardized baseline BCR-ABL/ABL transcript level.

About 16.0% of the studied patients showed CMR which was detected by the complete absence of the baseline BCR-ABL/ABL transcript (undetectable) and 18.0% had achieved Major molecular response (MMR) in which ≥ 3 log reductions from the baselines BCR-ABL/ABL transcript level.

The remainder patients (22.0%) showed suboptimal response while (18.0%) failed to achieve early molecular response either due to drug intolerance or resistance, progression to CML blast crisis or patient demise (Table 7).

The percentage of chronic phase CML patients with OS at 18 months follow-up was 88.0%. This percentage was not significantly differing among male patients (85.7%) or female patients (89.7%).

Discussion

Leukemia in general is a second common cancer in males and the fifth one in females in southern governments of Yemen with male to female ratio about 1.6:1 and a median age at diagnosis 22.5 years for males and 23 for females ranging from 2-79 years old.

The age specific incidence rate for males is 8.6/100,000 at the age group (50-59) years and 9.9/100,000 of females observed at (50-59) years age group [12]. While according to GLOBOCAN 2012 among the different types of cancer, leukemias appear to have a worldwide incidence about 4.7/100,000 in general. It was found to be in more developed countries about 4.7/100,000 versus 3.8/100,000 of population in less developed countries [13]. In Yemen there is a lack of national statistical studies concerned with incidence and prevalence of chronic myeloid leukemia. Previous local studies showed that CML consisting about 21.7% of adult leukemia according to Abdul Hamid (2015) [14] which is almost near to the results in western countries since that according to united states Surveillance Epidemiology and End Results data (http://WWW.seer.cancer.go) CML account for 20% of all adult leukemia [15]. The incidence is lower in Saudi Arabia where CML account for 16% of leukemia cases [16].

European Leukemia Net experts panel 2013 states a recommendations for follow up and assessed treatment in chronic myeloid leukemia patients treated with TKI based on assessment of hematological, cytogenetic and molecular response of patients.

Optimal hematological response reflect platelets count <450 × 10^9/L, WBC count <10 × 10^9/L with differential count without immature granulocyte, with less than 5% basophiles and non palpable spleen [17].

In current study there were impressive rate of hematological response one month after starting imatinib despite late presentation in most cases of chronic phase.

Hence hematological profile prior to imatinib showed a mean hemoglobin value about 10.2 gm/dL WBC 65.7 × 10^9/L, ANC 29.2 × 10^9/L and 448.2 × 10^9/L platelets count, significant improvement in blood picture was observed mainly of WBC, ANC and platelets count where marked reduction was reported with 9.5 × 10^9/L, 5.65 × 10^9/L and 246.2 × 10^9/L respectively (p=0.001), while haemoglobin value didn't show any improvement, this could be due to complexity of underlying causes in addition to disease

Parameter	Baseline (n=50)	Female (n=29)	*p*-value
	Mean ± SD Median (Min.-Max.)	Mean ± SD Median (Min.-Max.)	
Hemoglobin concentration (g/dl)	10.2 ± 1.8 9.9 (6.3-14.3)	10.3 ± 1.9 9.8 (6.8-15.2)	0.603
Total WBCs count (X10^9/L)	65.7 ± 60.2 40.0 (4.6-290.0)	9.5 ± 12.3 5.05 (1.8-61.0)	**0.0001***
Platelets count (X10^9/L)	448.2 ± 230.7 445.0 (54.0-1090	246.2 ± 150.7 222.5 (35.0-1083)	**0.0001***
Differential count of peripheral blood smear			
Neutrophils (%)	45.2 ± 17.7 42.0 (18.0-82.0)	50.1 ± 14.2 50.5 (23.0-80.0)	0.108
Eosinophils (%)	4.9 ± 3.6 4.0 (1.0-18.0)	3.9 ± 2.4 4.0 (0.0-12.0)	0.149
Basophils (%)	2.1 ± 1.1 2.0 (1.0-6.0)	3.1 ± 2.5 2.0 (0.0-12.0)	0.126
Lymphocytes (%)	10.7 ± 9.5 9.0 (2.0-51.0)	33.8 ± 14.8 33.5 (1.0-75.0)	**0.0001***
Monocytes (%)	3.3 ± 3.1 2 (1.0-12.0)	4.4 ± 2.3 5.0 (0.0-11.0)	0.546
Myelocytes (%)	18.1 ± 7.4 18.0 (3.0-31.0)	5.0 ± 3.6 3.5 (0.0-12.0)	**0.001***
Metamyelocytes (%)	8.6 ± 6.1 8.0 (2.0–21.0)	5.4 ± 3.5 5.0 (0.0 –11.0)	**0.032***
Band form (%)	11.3 ± 6.3 10.0 (3.0-28.0)	7.2 ± 4.0 7.0 (0.0–17.0)	**0.001***
ANC (X10^9/L)	29.2 ± 37.9 15.75 (1.4–176.9)	5.6 ± 9.2 2.56 (0.7–48.0)	**0.0001***

WBC: White blood cells; ANC: Absolute neutrophils count
**p*-value is statistically significant
Table 4: Comparison between the baseline and after one month hematological findings of the studied patients with chronic myeloid leukemia

BCR-Abl/Abl ratio (%)	Male (n=21)	Female (n=29)	Total (n=50)	*p*-value
	Mean ± SD Median (Min.-Max.)	Mean ± SD Median (Min.-Max.)	Mean ± SD Median (Min.-Max.)	
Baseline at diagnosis	2.82 ± 3.29 (0.02-10.92)	2.93 ± 5.18 (0.00-23.03)	2.88 ± 4.45 (0.00-23.03)	0.932
After 3 months of treatment	0.48 ± 1.53 (0.00–7.05)	1.55 ± 3.90 (0.00-17.82)	1.06 ± 3.07 (0.00-17.82)	0.247
p-value	**0.005***	0.257	**0.023***	0.457

**p*-value is statistically insignificant
Table 5: The mean BCR-Abl/Abl at baseline and after one month according to sex of patients with chronic myeloid leukemia

Item	Male (n=21)	Female (n=29)
	No.	No.
Complete molecular response (CMR) Undetectable	8	16.0
Major molecular response(MMR) ≥ 3 log reduction	9	18.0
Optimal early molecular response(EMR) ≥ 1 log reduction but <3 log reduction	13	26.0
Suboptimal response <1 log reduction but more than standardized baseline	11	22.0
Failure (no molecular response)	9	18.0

Table 6: Results of early molecular response in the studied patients with chronic myeloid leukemia at 3 months

Overall survival at 18 months	Male (n=21)		Female (n=29)		Total (n=50)	
	No.	%	No.	%	No.	%
Yes	18	85.7	26	89.7	44	88.0
No	3	14.3	3	10.3	6	12.0

p-value = 0.499 is considered statistically insignificant

Table 7: Percentage of chronic myeloid leukemia patients with overall survival at 18 months by sex

process by itself including nutritional factors, predominance of female gender in this study with pre-existing anemia secondary to previous pregnancies and/or menstrual blood loss, in addition to therapy hematological side effects .

Optimal hematological response was achieved in 84% of our patients, while only 14% of them failed to show any response, in 2% of patients normalization of blood picture was achieved with regression of splenomegaly which still palpable, this rate reflect potency of targeted therapy.

This result was approximately closed to data reported from Patan hospital in India where optimal hematological response rate was 78% [18], but lower than those reported in Asia including China, Hong Kong, India and Southern Korea with 98%, 100%, 96%, and 100% optimal hematological response respectively [19], and lower than data reported from Brazil (95%) [20], Portugal (95.4%) [21], Malaysia (93.2%) [22], and Tanzania (91.3%) [23]. where optimal hematological response reached at the end of three months following starting therapy.

Optimal early molecular response (EMR) reflecting achievement of ≥ 1 Log reduction of BCR-ABL level from the standardized base line value after 3 months of initiating TKI which is corresponding to <10% (IS: International scale).

In current study median BCR-ABL ratio at diagnosis was 120%, three months later significant reduction was observed with a median BCR-ABL ratio became 2%. (p=0.001) versus median BCR-ABL/GUS ratio at diagnosis about 15.5% then reduced to 0.62% after three months according to Benjamin Hanfstein et al. report (2014) [24].

Early assessment of molecular response three months after starting TKI (imatinib in our study) has become an important tool to predict favorable outcome.

Optimal early molecular response was reached in 60% of patients i.e ≥ 1 log reduction of standardized base line BCR-ABL ratio which found to be 72% in our study, this ≥ 1 log reduction is equal to ≤ 10% (IS: International scale) according to European LeukemiaNet (ELN)) [25].

Concerning Progression free survival (PFS), the percentage of CP-CML patients with PFS at 18 months follow up was 86.0%, showing significant higher mean PFS of (18.0 months) for those who obtained optimal early molecular response at three months when compared to those obtained suboptimal (16.4 months) and those who failed to achieve early molecular response (16.2 months) at three months, with significant statistical differences (p=0.007), while overall survival at 18 months was found in 88.0% of CML patients.

References

1. Melo JV. The molecular biology of chronic myeloid leukaemia. Leukemia. 1996 May;10(5):751-756.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010 Sep-Oct;60(5):277-300.
3. Dewald GW, Juneau AL, Schad CR, Tefferi A. Cytogenetic and molecular genetic methods for diagnosis and treatment response in chronic granulocytic leukemia. Cancer Genet Cytogenet. 1997 Mar;94(1):59-66.
4. Garcia-Manero G, Faderl S, O'Brien S, Cortes J, Talpaz M, et al. Chronic myelogenous leukemia: a review and update of therapeutic strategies. Cancer. 2003 Aug;98(3):437–457.
5. Chase A, Huntly BJ, Cross NC. Cytogenetics of chronic myeloid leukaemia. Best Pract Res Clin Haematol. 2001 Sep;14(3):553-571.
6. Cramer E, Auclair C, Hakim J, Feliu E, Boucherot J, et al. Metabolic activity of phagocytosing granulocytes in chronic granulocytic leukemia: ultrastructural observation of a degranulation defect. Blood. 1977 Jul;50(1):93-106.
7. Silver RT. Morphology of The Blood And Marrow In Clinical Practice. New York, NY: Grune & Stratton. 1970:84.
8. Buyukasik Y, Haznedaroglu I, Ilhan O. Chronic Myeloid Leukemia: Practical Issues in Diagnosis, Treatment and Follow-up. International Journal of Hematology and Oncology. 2010; 20(2).
9. Hamid GA. Target therapy and monitoring of chronic myeloid leukemia. World J Pharm Res. 2015 Sep;4(9):391-405.
10. Wang L, Pearson K, Ferguson JE, Clark RE. The early molecular response to imatinib predicts cytogenetic and clinical outcome in chronic myeloid leukaemia. Br J Haematol. 2003 Mar;120(6):990-999.
11. Branford S, Fletcher L, Cross NC, Müller MC, Hochhaus A, et al. Desirable performance characteristics for BCR-ABL measurement on an international reporting scale to allow consistent interpretation of individual patient response and comparison of response rates between clinical trials. Blood. 2008 Oct;112(8):3330-3338.
12. Cancer Incidence report 2007-2011. Aden Cancer Registry and Research. 2013 Oct;Part 2:16.
13. GLOBOCAN 2012 estimated cancer incidence and prevalence worldwide in 2012 v1.0. IARC CancerBase No. 11.
14. Hamid GA, Al-Nabehi A. Clinicoepidemiological features of adult leukemias in Aden, Yemen Article in Indian Journal of Applied Research. 2015 Jul;5(7):20.
15. United States surveillance epidemilogy and end result data. National Cancer Institute, Geneva, Switzerland.

16. Al Bakr R, Kojah O. Incidence trend of the leukemia Reported cases in the Kingdom of Saudi Arabia, Observational descriptive Statistic from Saudi Cancer Registry. IJBR. 2014 Aug;5:8.
17. Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2006 Sep 15;108(6):1809-1820.
18. Kayastha GK, Gurung P, Acharya PK, Paudyal BP, Hayes B, et al. Patan hospital experience in treating philadelphia chromosome/ BCR-ABL1 positive chronic myeloid leukemia patients with gleevec (imatinib mesylate); the first generation specific tyrosine kinase inhibitor. BMC Blood Disord. 2010 Dec;10:8.
19. Au WY, Caguioa PB, Chuah C, Hsu SC, Jootar S, et al. Chronic myeloid leukemia in Asia. Int J Hematol. 2009 Jan;89(1):14-23.
20. Machado MP, Tomaz JP, Lorand -Metze I, de Souza CA, Bendit I, et al. Monitoring of BCR-ABL levels in chronic myeloid leukemia patients treated with imatinib in the chronic phase- the importance of a major molecular response. Rev Bras Hematol Hemoter. 2011;33(3):211-215.
21. Mendes A. Evaluation of treatment response to imatinib in patients diagnosed with chronic myeloid leukemia.
22. Bee PC, Gan GG, Tai YT, Haris AR, Chin E, et al. An update on imatinibmesylate therapy in chronic myeloid leukaemia patients in a teaching hospital in Malaysia. Singapore Med J. 2012 Jan;53(1):57-61.
23. Tebuka E, Makubi A and Khamza M. Complete hematologicl response to imatinib in chronic myeloid leukemia patients attending the Ocean Road Cancer Institute in Tanzania. Tanzania Journal of Health Research. 2016 Oct;18(4).
24. Shlyakhto V, Lauseker M, Hehlmann R, Saussele S, Dietz C, et al. Velocity of early BCR-ABL transcript elimination as an optimized predictor of outcome in chronic myeloid leukemia (CML) patients in chronic phase on treatment with imatinib. Leukemia. 2014 Oct;28(10):1988-1992.
25. Hantschel O, Rix U, Superti-Furga G. Target spectrum of the BCR-ABL inhibitor imatinib, nilotinib and dasatinib. Leuk Lymphoma. 2008 Apr;49(4):615-619.