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CYTOGENETIC AND MOLECULAR RESPONSE AFTER TREATMENT WITH TYROSINE KINASE INHIBITOR IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA IN MARJAN MEDICAL CITY

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ABSTRACT

Background: Chronic myeloid leukaemia (CML) is a stem cell disorder characterised by an acquired chromosomal abnormality known as the Philadelphia chromosome. It is likely that stopping BCR-ABL will be very important for the treatment to work. Tyrosine kinase inhibitors have significantly altered the prognosis of chronic myeloid leukaemia (CML). **Methods:** This retrospective study encompassed all patients with CML, in chronic, accelerated phase, and blast crisis, who received treatment with imatinib and nilotinib at Marjan Medical City in Babylon, aimed at evaluating the cytogenetic and molecular response to therapy. **Results:** A total of 115 patients with CML participated in a government-sponsored national program. Imatinib was the first drug given to all of the patients. After a median follow-up of 44 months, 80% had a major cytogenetic response, and 67% had a major molecular response. The rates of event-free survival, overall survival, and progression-free survival after five years were 82%, 97%, and 93%, respectively. A total of 38 patients (33%) were transitioned to Nilotinib; 27 patients attained MMR, while 9 patients exhibited no response. **Conclusion:** This study demonstrated that imatinib, administered as the first-line treatment for CML patients in Marjan Medical City, was well tolerated and produced results comparable to those observed in certain Iraqi Kurdistan and Western studies. Molecular monitoring significantly influenced treatment decisions. This study has validated that nilotinib is an efficacious treatment for imatinib-resistant cases and was necessary in one-third of patients, yielding favourable outcomes.

KEYWORD: Chronic Myeloid Leukaemia, Tyrosine Kinase Inhibitor, Complete Cytogenetic Response, Major Molecular Response.

INTRODUCTION

Chronic myeloid leukemia (CML) is a malignant clonal disorder of hematopoietic stem cells characterized by the expansion of myeloid, platelet, and erythroid series in peripheral blood and by prominent myeloid hyperplasia in the bone marrow.[1] Unlike certain other leukemias, there is no evidence of familial association in CML, and monozygotic twins do not exhibit increased concordance. Most environmental or occupational exposures, such as benzene, insecticides, fertilizers, or viral infections, are not strongly linked to CML. The notable exception is ionizing radiation, which increases risk in a dose-dependent manner.[2] CML is an acquired hematopoietic stem cell disease with a distinct cytogenetic hallmark: the reciprocal translocation between chromosomes 9 and 22, t(9;22), described as the Philadelphia chromosome by Nowell and Hungerford. This translocation relocates the abl oncogene from chromosome 9 to the breakpoint cluster region (BCR) of chromosome 22, resulting in the BCR-ABL fusion gene.[3] The gene encodes a constitutively active tyrosine kinase protein that drives abnormal cell proliferation and survival. In some cases, a reciprocal ABL-BCR fusion also occurs, and deletions around the junction site have been documented in 10–15% of patients, often contributing to disease progression. Although the molecular events following BCR-ABL fusion are well defined, the initiating mechanism of translocation remains unclear. Genetic

instability resulting from BCR-ABL activity is believed to contribute to secondary mutations, particularly in the blast crisis phase.[4] Clinically, CML typically affects adults in their fourth and fifth decades of life, although younger patients may present with more aggressive disease forms. It often begins insidiously and is discovered incidentally during routine blood counts revealing leukocytosis or upon detection of splenomegaly.[5,6] Common symptoms include fatigue, weight loss, early satiety, and left upper quadrant pain due to splenic infarction. Splenomegaly is the most frequent physical finding, occurring in over half of patients, and its degree often correlates with disease activity. Hepatomegaly may also occur, while leukostasis and hyperviscosity are complications of markedly elevated leukocyte counts. Retinal hemorrhages and venous obstruction can be observed in advanced cases.[7,8] CML is classically divided into three phases: chronic, accelerated, and blast crisis. Most patients (approximately 85%) are diagnosed during the chronic phase, which is relatively indolent. Without treatment, disease progression to the accelerated and subsequently blast phase is inevitable, mirroring acute leukemia with poor prognosis.[9–11] This triphasic course highlights the importance of early recognition, appropriate diagnostic evaluation, and timely therapy to improve survival outcomes.

SUBJECTS AND METHODS

This observational, retrospective study encompassed all patients diagnosed with CML and treated with imatinib and nilotinib at Marjan Medical City from April 2005 to November 2016, totalling 115 patients with Ph-positive CML. At diagnosis and follow-up, all patients had peripheral blood cytogenetic FISH tests. They were all treated with Imatinib 400mg/day orally and/or Nilotinib 300 mg twice daily (in case of resistance) orally as part of a government-sponsored national program. The molecular monitoring, however, was done on a regular basis starting in 2012. Fluorescence in situ hybridisation (FISH) analysis studies on peripheral blood were used to check for cytogenetic response every six months until the patient reached a complete cytogenetic response (CCyR), and then every year. The FISH analysis was conducted at the laboratory of hematopathology and immunology in Karbala, Iraq, utilising a dual color-dual fusion kit from Applied Meta-system (Germany). A complete cytogenetic response (CCYR) occurs when there are no Ph-positive cells (0%), a partial cytogenetic response (PCyR) occurs when there are 1–34% Ph-positive cells, a minor cytogenetic response occurs when there are 35–65% Ph-positive cells, and no response occurs when there are more than 65% Ph-positive cells. The major cytogenetic response was the sum of both complete and partial cytogenetic responses.[12] Molecular monitoring was conducted by quantifying the number of BCR-ABL transcripts in the peripheral blood. This was accomplished utilising reverse transcription-polymerase chain reaction (RT-PCR) in the haematology laboratory in Karbala, Iraq, adhering to international standards. A BCR-ABL/ABL ratio of less than 0.1% IS (international scale) was used to define major molecular response (MMR). A complete molecular response, on the other hand, meant that RT-PCR could not find any BCR-ABL transcripts. The endpoints for survival in our study are: A- Event-free survival (EFS): the time between the start of treatment and any of the following events; 1. Loss of total haematological response 2. loss of major cytogenetic response (MCyR) 3. Moving on to the accelerated phase or blast crisis 4. Death B. progression-free survival (PFS): the time between the start of treatment and the start of the follow-up period, when the patient moved to the accelerated phase or blast crisis. C. Overall survival (OS): the time between diagnosis and the last follow-up. Statistical analysis was conducted utilising SPSS version 20. We showed categorical variables as both frequencies and percentages. Continuous variables were expressed as (Means ± SD). The Student t-test was employed to compare the means of two groups. The Wilcoxon Signed Ranks Test was employed to compare means for paired readings when the differences were not normally distributed. We used Pearson's chi square (X2) and Fisher's exact test to find the relationship between categorical variables. A p-value of ≤ 0.05 was deemed significant.

RESULTS

The mean age of our patients in Marjan Medical City according to socio-demographic characteristics was (40.87± 15.73) which included 65 females (64 adult females with 1child female at 5years old) and 50 males (47 adult males with 3child males at 1,4,9 years). As in table 1.

Table 1: Distribution of patients according to socio-demographic characteristics.

Socio-Demographic Characteristics		
Age (years)	**(40.87 ±15.73)**	**(1-75)**
Gender		
Male	50	43.5%
Female	65	56.5%
Total	115	100.0%

According to the phases of disease 107 patients was in chronic phase, 6 patients in accelerated phase and 2 patients in blast crisis. Figure 1 shows distribution of patients with Chronic Myeloid Leukemia according to phases of disease. Majority (93%) of patients presented with chronic phase.

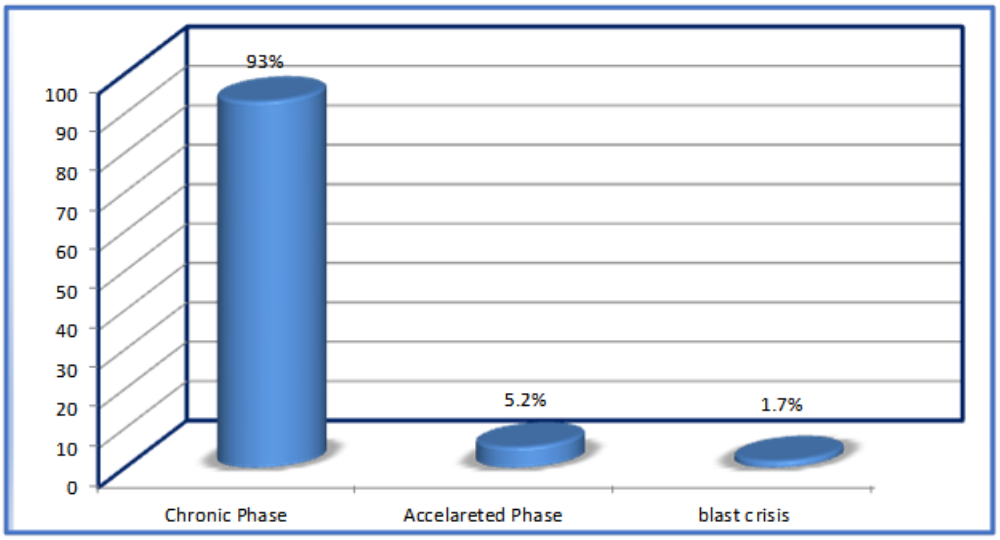

Figure 1: Distribution of patients according to phases of disease.

Response and Outcome

Cytogenetic response After a duration of treatment which range from (8-126) months, median duration was 44.2 months the distribution of patients with Chronic Myeloid Leukemia according to Cytogentic response measured by FISH study for PH chromosome after 12 months of Imatinib was (52.2%) of patients presented with complete cytogenetic response, (27.8%) partial cytogenetic response, (12.2%) minor response and (7.8%) no response. Major cytogenetic response which includes complete and partial response (80%) As shows in Figure 2.

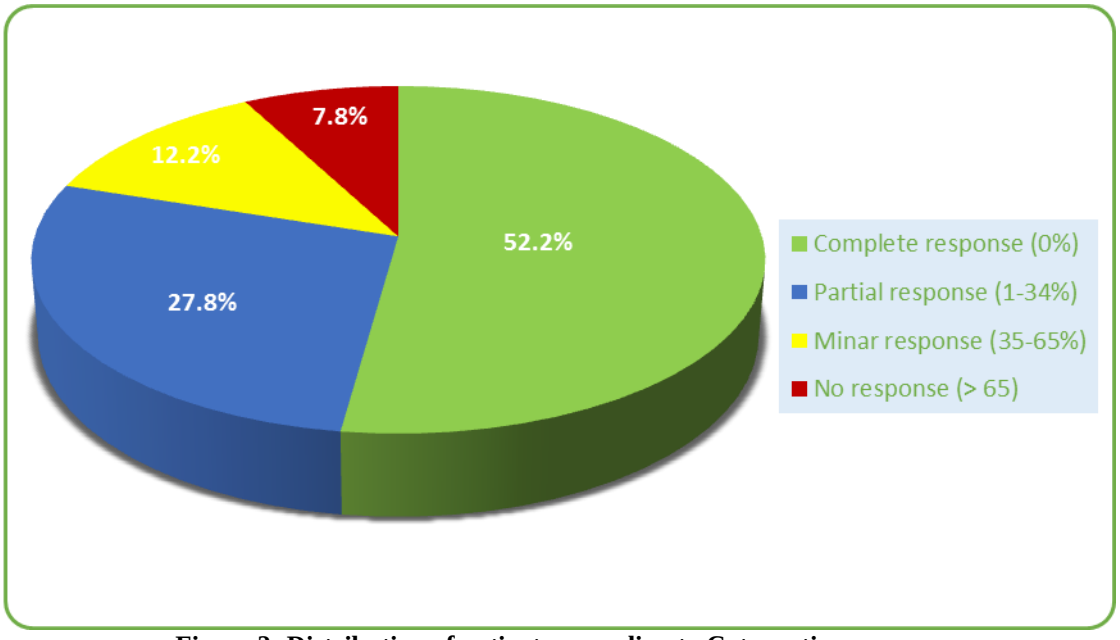

Figure 2: Distribution of patients according to Cytogentic response.

Molecular Response: Reverse transcription-polymerase chain reaction (RT-PCR) was first introduced in Iraq after 2012. After more than 12 months of last follow up from imatinib treatment, 77patients (67%) had major molecular response included 2 patients in accelerated phase, while 38 patients (33%) failed to achieve (MMR) included 4 patients in accelerated phase and 2 patients in blast crisis. 38 of patients whose their treatment was change to nilotinib, MMR was achieved in 27 patients, 2 of them in accelerated phase while 9 patients failed to response. Figure 3 shows distribution of patients with Chronic Myeloid Leukemia according to major molecular response (MMR): >3 log reduction, <0.1%IS in BCR-ABL\ABL ratio measured by RT-PCR after >12 month of Imatinib and >12 months of Nilotinib (in those failed to response to imatinib).

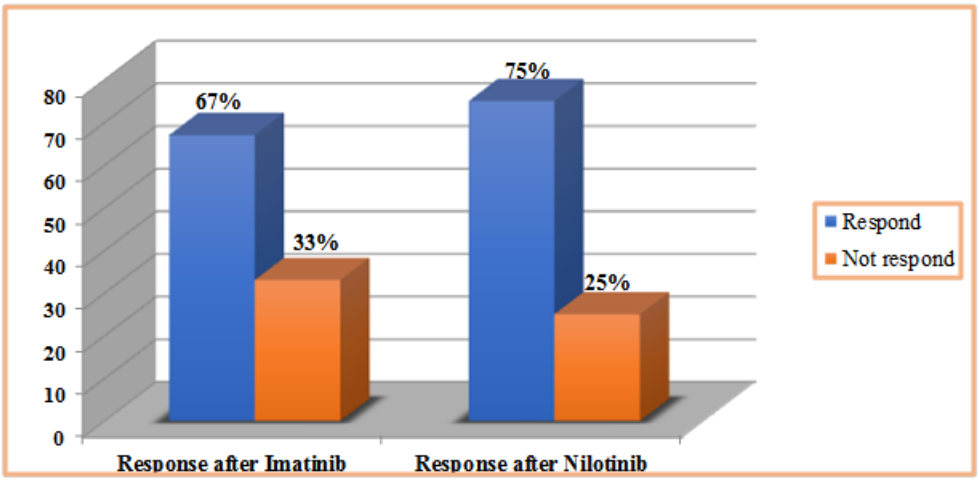

Figure 3: Distribution of patients according to major molecular response.

The Mean Differences of PH Chromosome Before and After Using of 12 Month Imatinib: Table 2 shows mean differences of PH chromosome before and after using of 12 month Imatinib for the patients with Chronic Myeloid Leukemia. There were significant differences between means of PH chromosome by study groups.

Table 2: The mean differences of by PH chromosome before and after using of 12-month Imatinib.

Study variable	Study groups	N	Mean	Z	P value
PH chromosome (%)	At time of diagnosis	115	92.93 ± 7.25	**-9.309**	**<0.001***
	After 12 months of treatment	115	14.86 ± 24.2		

*p value ≤ 0.05 was significant. Wilcoxon Signed Ranks Test.

The Mean Differences of Age by Molecular Response to Imatinib

Table 3 shows mean differences of age by molecular response to Imatinib for the patients with Chronic Myeloid Leukemia. There were no significant differences between means of age by study groups.

Table 3: The mean differences of age by molecular response to Imatinib.

Study variable	Study groups	N	Mean	t-test	P value
Age (years)	Respond	77	41.42 ± 16.03	0.532	0.596
	Not respond	38	39.76 ± 15.28		

*p value ≤ 0.05 was significant.

The Association between Molecular Response to Imatinib and Study Variables

Table 4 shows the association between molecular response to Imatinib and study variables including (gender and phases of disease). There was significant association between molecular response to Imatinib and phases of disease.

Table 4: Association between molecular response to Imatinib and study variables.

Study variables	Response to Imatinib		χ^2	P-value
	Respond	Not respond		
Gender				
Male	37 (48.1)	13 (34.2)	1.984	0.159
Female	40 (51.9)	25 (65.8)		
Total	77 (100.0)	38 (100.0)		
Phases of disease				
Chronic phase	75 (97.4)	32 (84.2)		
Accelerated phase	2 (2.6)	4 (10.5)		**0.022*[f]**
Blast crisis	0 (0.0)	2 (5.3)		
Total	77 (100.0)	38 (100.0)		

*p value ≤ 0.05 was significant. Fisher-exact test.

The Mean Differences of Age by Molecular Response to Nilotinib

Table 5 shows mean differences of age by molecular response to Nilotinib for the patients with Chronic Myeloid Leukemia. There were no significant differences between means of age by study groups.

Table 5: The mean differences of age by molecular response to Nilotinib.

Study variable	Study groups	N	Mean	t-test	P value
Age (years)	Respond	27	39.55 ± 15.44	- 0.69	0.495
	Not respond	9	43.33 ± 9.16		

*p value ≤ 0.05 was significant.

The Association between Molecular Response and Study Variables: Table 6 shows the association between molecular response to Nilotinib and study variables including (gender and phases of disease). There was significant association between molecular response to Nilotinib and phases of disease.

Table 6: Association between molecular response to Nilotinib and study variables.

Study variables	Response to Nilotinib		χ^2	P-value
	Respond	Not respond		
Gender				
Male	11 (40.7)	1 (11.1)	1.984	0.219
Female	16 (59.3)	8 (88.9)		
Total	27 (100.0)	9 (100.0)		
Phases of disease				
Chronic phase	25 (92.6)	5 (55.6)		
Accelerated phase	2 (7.4)	2 (22.2)		**0.012*[f]**
Blast crisis	0 (0.0)	2 (22.2)		
Total	27 (100.0)	9 (100.0)		

*p value ≤ 0.05 was significant. Fisher-exact test.

Survival: Median follow up period of 5 years, the event free survival (EFS) for CML patients on TKI was 82 %, overall survival (OS) rates 97%, progression- free survival (PFS) 93%.

DISCUSSION

In our study, we evaluated 115 patients with chronic myeloid leukemia (CML) from Marjan Medical City, Babylon, after excluding those with irregular follow-up. All patients received imatinib, and a major cytogenetic response (MCR) was achieved in 80% of cases, with complete cytogenetic response (CCyR) in 52.2% and partial response in 27.8%, after a median follow-up of 42 months. These findings are comparable to results from Iraqi Kurdistan by Ali MD et al.[13], who reported an MCR rate of 79% after a median follow-up of 35 months. Similarly, Guilhot et al.[14] reported an MCR of 78% after 12 months in the USA, while Dhahi M.A.R. et al.[15] in Baghdad documented a 71% MCR after 24 months of follow-up. In contrast, a study from Egypt by Mervat M. Omar[16] observed lower responses (MCR 58%, CCyR 32%) after 12 months, likely due to the smaller cohort (23 patients). A large European study by Hasford J. et al.[17] reported even higher responses, with MCR achieved in 85% of patients after 18 months of follow-up. Molecular monitoring of CML patients in Iraq was initiated in 2012, and annual follow-up with molecular response assessment has since continued. In our cohort, 67% of imatinib-treated patients achieved a major molecular response (MMR) after at least 12 months of therapy, consistent with outcomes from Malaysia reported by Ping Chong Bee et al.[18], where MMR was 65.7% after 18 months. Comparable results were also observed in Japan by Yasuhito Nannya et al.[19], who documented a 71.4% MMR rate after 24 months. In contrast, Ali MD et al.[13] reported a lower MMR rate of 38% after 12 months of treatment, possibly reflecting shorter follow-up duration. Failure to achieve CCyR within the first 12 months of imatinib therapy was associated with a higher risk of disease progression and a reduced probability of achieving MMR. Among our patients, 38 individuals (33%) who failed to respond to imatinib were switched to second-line therapy with nilotinib (Tasigna). Of these, 27 patients (75%) achieved MMR. This result is more favorable compared to Boquimpani C. et al.[20] in Brazil, who reported an MMR rate of 54% after a median of 35 months in imatinib-resistant patients, and Ali MD et al.[13], who reported only 24% after 12 months of nilotinib, likely due to smaller patient numbers and shorter follow-up. No significant association between age or gender and treatment response was identified in our study, consistent with findings from Gugliotte G. et al.[21] in Italian patients, where both younger and older groups demonstrated similar responses to TKI therapy. Long-term outcomes in our cohort were favorable, with event-free survival (EFS) of 82%, progression-free survival (PFS) of 93%, and overall survival (OS) of 97% after a median of five years. These findings are in line with results reported by Cervantes F. et al.[22] in European patients after five years and by Jiang et al.[23] in Chinese patients after seven years of follow-up.

CONCLUSION

This study showed that in Marjan Medical city, imatinib provided as first line treatment for CML patients, was well tolerated and yielded results comparable to some degree in Iraqi Kurdistan and Western studies. Molecular monitoring had an important effect on treatment decisions. This study has confirmed that nilotinib is an effective treatment for imatinib resistant cases and was needed in one third of patients with good results. Nilotinib more potent with lower failure rate than imatinib therefor better to use as first line treatment in patients with CML.

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