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Research Article

Assessment of the Early Reachability of Major Molecular Response (MMR) in Chronic Phase of CML Patients on First and Second Generation Tyrosine Kinase Inhibitors (TKI): As Regard 1st and 2nd Line of Treatment

Mohamed AbdAllah Shazly*, Mohamed Osman Azzazi, Rasha Magdy Mohamed Said, Amina Ahmed Mohamed Allam

Department of Internal Medicine and Clinical Hematology, Ain Shams University, Cairo Governorate, Egypt

ABSTRACT

Background: CML treatment changed with the development of Tyrosine Kinase Inhibitors (TKIs) that interfered with the interaction between the *BCR-ABL* oncoprotein and Adenosine Triphosphate (ATP), blocking malignant clone proliferation.

Aim: To assess early reachability of Major Molecular Response (MMR) of CML patients in chronic phase on first and second generation TKI.

Patients and methods: MMR was assessed by quantitative PCR for *BCR-ABL* in 100 patients with newly diagnosed CML divided to three groups: First enrolled 40 patients on first generation TKI (imatinib) second enrolled 40 patients shifted from first generation (imatinib) to second generation (nilotinib) and third enrolled 20 patients on second generation (nilotinib) from the start. Patients were recruited from hematology department; Ain shams university hospital over the period from January 2018 to January 2019 and followed for 1 year.

Results: MMR at 12 months of treatment on nilotinib (first line) was higher than other groups (p= 0.025). Patients treated with imatinib 400 mg with additional cytogenetic abnormalities had high numbers of MMR failure (p=0.001) when compared to patients on nilotinib either 1st line or shifted. Patients with high SOKAL score started on imatinib 400 mg had high number of MMR failure in comparison to patients on nilotinib 300 mg (p<0.001). Complete Cytogenetic Response (CCR) at 6 and 12 months was higher in patients on nilotinib 300 mg than imatinib 400 mg (p=0.020).

Conclusion: Treatment with nilotinib as first line had better outcome than starting with imatinib or switching to nilotinib.

Keywords: Chronic myeloid leukemia; Imatinib; Nilotinib

INTRODUCTION

Chronic Myeloid Leukemia (CML) is myeloproliferative disease. Clonal cells in CML originate from a pluripotent hematopoietic progenitor cell (stem cell) that exhibits growth advantage over normal hematopoietic progenitors. Leukemic progenitors in CML (chronic phase) have the capacity to undergo differentiation and maturation similar to normal cells. Therefore, almost all (immature and mature) cells of myeloid origin (granulocytes, erythroid cells, macrophages) and even B lymphocytes (but not T cells in most cases) are clonal in nature and exhibit the Philadelphia (Ph) chromosome in patients with CML [1]. Busulfan (BUS) and Hydroxyurea (HU) as cytoredution and interferon were primarily used as the first effective treatments for Chronic Myeloid Leukaemia (CML). The quality of life during the chronic phase (CP) of the disease was significantly improved thanks to this therapy, but it had only a modest impact on overall survival. Neither did it stop the progression

Correspondence to: Mohamed AbdAllah Shazly, Department of Internal Medicine and Clinical Hematology, Ain Shams University, Cairo Governorate, Egypt, E-mail: shazlyhematology@yahoo.com

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of the disease towards the accelerated and Blastic Phases (AP, BP) (OS). Because around 50% of the patients who were eligible for allogeneic Stem Cell Transplantation (allo SCT) developed into Philadelphia-negative, allo SCT constituted the first significant advancement in the development and prognosis of CML [2].

Symptoms are not specific, including weight loss, asthenia, fever, sweats, and malaise, in 40% of cases the diagnosis is based on abnormal blood counts and differential. Physical findings consist mainly splenomegaly in >50% of patients. The hallmark of diagnosis is leukocytosis with basophilia and with immature granulocytes, metamyelocytes, myelocytes and promyelocytes, and few or occasional myeloid blasts. Severe anemia is rare. Thrombocytosis is frequent. Prognosis can be assessed by calculating (SOKAL) score which need (Age, spleen size, platelet count and peripheral blood blasts). Peripheral blood eosinophil and basophil percentage also required for (Hasford) score (Euro score) [3]. The diagnosis must be confirmed by cytogenetics showing t (9;22)(q3.4;q1.1), and by reverse transcriptase polymerase chain reaction (RT-PCR) showing BCR-ABL transcripts. Also, Interphase Fluorescence *in Situ* Hybridization (I-FISH) of blood cells, using dual color dual fusion probes that allow the detection of (BCR-ABL) nuclei can be used [4].

A new, hybrid, fusion gene (BCR-ABL) is created as a result of the translocation of the ABL gene from chromosome 9 to chromosome 22 t (9;22)(q3.4;q1.1). This gene codes for an oncoprotein (P210, more rarely P190 or P230), which is found in the cytoplasm and has strong tyrosine kinase activity. This activation of several signals causes stem cells to undergo transformation. Due to the genetic instability of BCR-ABL positive cells, which are predisposed to various and heterogeneous genomic aberrations, the leukemic phenotype might change from chronic to acute [5]. The Food and Drug Administration (FDA) gave its blessing to imatinib mesylate as the first Tyrosine Kinase Inhibitor (TKI) for the treatment of CML-CP patients. It works by inhibiting phosphorylation of proteins involved in cell signal transduction through competitive inhibition at the ATP-binding region of the BCR-ABL protein. In addition to blocking the platelet-derived growth factor receptor and the C-KIT tyrosine kinase, it effectively inhibits the BCRABL kinase [6].

Even while imatinib produced some excellent benefits, only 55% of patients were still receiving treatment at the end of the 8-year follow-up period. This emphasised the need for other treatment choices for individuals who had tried imatinib unsuccessfully or were intolerant to it. Due to this, second generation TKIs were rationally developed with the hopes that they would successfully treat patients who were unable to continue receiving imatinib therapy [7]. Though its affinity for the ATP binding site on BCR-ABL is up to 50 times stronger *in vitro*, nilotinib is a structural analogue of imatinib. Nilotinib first showed this potential to induce hematologic and cytogenetic responses in patients who had failed imatinib treatment [8]. Dasatinib is an oral, second generation TKI that is 350 times more potent than imatinib *in vitro*. It is a potent multikinase inhibitor targeting BCR-ABL, the SRC family of kinases (SRC, LCK, HCK, YES, FYN, FGR, BLK, LYN, FRK), receptor tyrosine kinases (c-KIT, PDGFR, DDR1 and 2, c-FMS, ephrin receptors), and TEC family kinases (TEC and BTK) and demonstrates activity against most imatinib-resistant BCR-ABL mutations [9].

METHODOLOGY

To assess the early reachability of Major Molecular Response (MMR) of CML patients in chronic phase on first and second generation TKI (as regard 1st and 2nd line of treatment)

This is a Cohort Prospective study was conducted on 100 CML patients were recruited from Clinical Hematology Department, Ain Shams University Hospital (Cairo, Egypt) over the period from January 2018 to January 2019 and followed for 1 year. The study was done according to the Ethics Committee of Faculty of Medicine, Ain Shams University.

Patients were subdivided into 3 subgroups

- Group 1: 40 patients on first generation TKI (Imatinib)
- Group 2: 40 patients shifted from 1st generation (Imatinib) to 2nd generation (Nilotinib)
- Group 3: 20 patients on 2nd generation (Nilotinib) from the start

Exclusion criteria

1. CML patients in accelerated or transformed phase
2. Any associated malignancy with CML

All participants underwent a thorough physical examination, a full history review, a complete blood count, blood chemistry (including liver and kidney function tests, serum electrolytes, and Lactate Dehydrogenase (LOH)), a bone marrow aspirate stained with the Giemsa stain, and an assessment of the blast percentage to determine the stage of CML (chronic phase 5% blasts, accelerated phase >5% and 20% blasts, blast phase.

Cytogenetic studies were performed on bone marrow by FISH technique (Fluorescent *in Situ* Hybridization) and karyotyping at the time of diagnosis. FISH is a cytogenetic technique that uses fluorescent probes that bind to only those parts of the chromosome with a high degree of sequence complementarity. PCR for BCR-ABL at the time of diagnosis performed by quantitative reverse transcriptase polymerase chain reaction.

Statistical methodology

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean ± Standard Deviation (SD). Qualitative data were expressed as frequency and percentage. P value greater than 0.05 was considered insignificant. P less than 0.05 were considered significant. P less than 0.01 were considered highly significant.

RESULTS

A statistically significant difference was detected at 12 months regarding MMR using PCR for *BCR-ABL* between the studied groups with the largest number of patients in the group used nilotinib (p=0.025). While no statistically significant difference was detected at 6 and 9 months between the 3 studied groups with p=0.162 and p=0.096 respectively (Table 1). A statistically

nonsignificant difference was detected between the 3 groups at 3 months and 9 months after treatment regarding detecting Ph chromosome (complete cytogenetic response) using FISH with p value 0.096 and 0.078 respectively, while a statistically significant difference was detected between the 3 groups at 6 and 12 months after treatment regarding detecting Ph chromosome with p values 0.020 and 0.015 respectively (Table 2).

In patients received imatinib as first line treatment with high SOKAL score showed a statistical significant difference with patients with low and intermediate score with p<0.001 regarding MMR after 12 months of treatment. This is in contrast to groups shifted to imatinib or was started on it as first line, where no statistical significant difference was detected between patients with high, intermediate and low SOCKAL score regarding MMR after 12 months of treatment with p values equal 0.205 and 0.122 respectively (Table 3). A highly statistically significant difference was detected in patients on imatinib reached MMR when compared to others not reached MMR (large number of patients) regarding additional cytogenetic abnormalities with p<0.001. The other groups showed no statistically significant difference between patients with additional cytogenetic abnormalities who reached MMR (large number of patients) and others not reached MMR with P=0.067 in group 1 and P=0.402 in group 2 (Table 4).

Regarding age and sex in relation to MMR after 12 months of treatment, no statistically significant difference was detected between the 3 studied groups with P values 0.0162 and 0.780 respectively (Tables 5 and 6). A statistically significant difference was detected after 12 months of treatment between the studied group regarding ALT (P=0.047), AST (P=0.038).Total bilirubin (p=0.040) and direct bilirubin (p=0.002) where the mean levels were elevated in the 3rd group in which nilotinib was the first line of treatment (Table 7). ECG changes after 12 months showed statistically significant difference between 3 groups where ECG changes were more in group 3 treated with nilotinib as first line(p=0.005) (Table 8).

Table 1: Comparison between studied groups regarding major molecular response (MMR) at 6,9 and 12 months of treatment.

MMR	Groups						Chi-square	
	Imatinib		Shifted		First line nilotinib			
	N	%	N	%	N	%	X^2	P-value
After 6 months	20	50	25	62.5	15	75	3.646	0.162
After 9 months	22	55	29	72.5	16	80	4.681	0.096
After 12 months	25	62.5	30	75	19	95	7.354	0.025

Table 2: Comparison between studied groups as regard complete cytogenetic response (Ph chromosome by FISH) at 6,9 and 12 month of treatment.

CCR	Groups						Chi-square	
	Group 1 imatinib		Group 2 shifted		Group 3 first line nilotinib			
	N	%	N	%	N	%	X^2	P-value
After 6 months	19	47.5	24	60	17	85	7.812	0.02
After 9 months	23	57.5	29	72.5	17	85	5.096	0.078
After 12 months	24	60	30	75	19	95	8.422	0.015

Table 3: Comparison between studied groups regarding SOKAL score either low, intermediate, high and MMR.

Groups	SOKAL score	MMR After 12 months						Chi-square	
		MMR reached		MMR not reached		Total			
		N	%	N	%	N	%	X^2	P-value
Group 1imatinib	Low	12	48.00	0	0.00	12	30.00	18.347	<0.001
	Intermediate	7	28.00	1	6.67	8	20.00		

	High	6	24.00	14	93.33	20	50.00		
	Total	25	100.00	15	100.00	40	100.00		
Group 2 shifted	Low	9	30.00	6	60.00	15	37.50	3.17	0.205
	Intermediate	7	23.33	2	20.00	9	22.50		
	High	14	46.67	2	20.00	16	40.00		
	Total	30	100.00	10	100.00	40	100.00		
Group 3 first line nilotinib	Low	3	15.79	1	100.00	4	20.00	4.211	0.122
	Intermediate	7	36.84	0	0.00	7	35.00		
	High	9	47.37	0	0.00	9	45.00		
	Total	19	100.00	1	100.00	20	100.00		

Table 4: Comparison between studied groups as regard additional cytogenetic abnormalities and MMR.

Groups	**Additional cytogenetic abnormalities**	**MMR After 12 months**						**Chi-square**	
		MMR reached		MMR not reached		Total			
		N	%	N	%	N	%	X^2	P-value
Group 1 Imatinib	Normal	19	76.00	0	0.00	19	47.50	21.714	<0.001
	Mutations	6	24.00	15	100.00	21	52.50		
	Total	25	100.00	15	100.00	40	100.00		
Group 2 shifted	Normal	14	46.67	8	80.00	22	55.00	3.367	0.067
	Mutation	16	53.33	2	20.00	18	45.00		
	Total	30	100.00	10	100.00	40	100.00		
Group 3 first line nilotinib	Normal	11	57.89	1	100.00	12	60.00	0.702	0.402
	Mutation	8	42.11	0	0.00	8	40.00		
	Total	19	100.00	1	100.00	20	100.00		

Table 5: Comparison between sex and Major Molecular Response (MMR).

Sex	**MMR after 12 months**				**Chi-square**	
	Positive		Negative			
	N	%	N	%	X^2	P-value
Male	29	39.19	11	42.31	0.078	0.78
Female	45	60.81	15	57.69		
Total	74	100.00	26	100.00		

Table 6: Comparison between age and MMR after 12 months.

MMR after 12 months	**Age**				**T-test**	
	N	Mean	±	SD	t	P-value
Positive	74	40.459	±	11.174	1.41	0.162
Negative	26	36.846	±	11.446		

Table 7: Comparison between studied groups regarding liver enzymes and bilirubin after treatment.

After 12 months		Groups									ANOVA	
		Group 1 imatinib			Group 2 shifted			Group 3 first line nilotinib			F	P-value
AST	Range	4	-	45	5	-	57	12	-	29	3.388	0.038
	Mean ± SD	14.3	±	7.936	19.025	±	12.487	20	±	4.623		
ALT	Range	8	-	55	7	-	117	16	-	52	3.151	0.047
	Mean ± SD	23.075	±	10.136	31.25	±	22.944	31.85	±	8.725		
Total bil.	Range	0.2	-	4	0.5	-	6.2	1	-	3.8	3.338	0.04
	Mean ± SD	1.195	±	1.003	1.71	±	1.252	1.825	±	0.687		
Direct bil.	Range	0.1	-	3.1	0.4	-	4.4	0.8	-	2	6.944	0.002
	Mean ± SD	0.628	±	0.637	1.128	±	0.853	1.195	±	0.324		

Table 8: Comparison between studied regarding ECG after 12 months of treatment.

ECG After 12 Months	Groups								Chi-square	
	Group 1 imatinib		Group 2 shifted		Group 3 first line nilotinib		Total			
	N	%	N	%	N	%	N	%	X^2	P-value
Normal	35	87.5	23	57.5	11	55	69	69	10.706	0.005
Abnormal	5	12.5	17	42.5	9	45	31	31		
Total	40	100	40	100	20	100	100	100		

DISCUSSION

In this study, there was no statistically significant difference between age of patient included in this study and early achievement of Major Molecular Response (MMR) (p=0.39).A Similar conclusion was obtained from Larson, et al. [8], where older patients in 12 month of follow-up, nilotinib demonstrated high rates of CCyR and MMR similar to those in younger patients however his results showed a superiority to nilotinib than imatinib. In this study, there was no statistically significant difference between sex of patients included in this study and early achievement of molecular response. This is inconsistent with what stated by Lin, et al. [10], where men had lower MMR rate than women (p value 0.006).

Patients in our study were divided into groups based on their SOKAL risk scores at the time of diagnosis. Age, spleen size, platelet count, and blast count are all factors that go into the SOKAL score. Low-risk (SOKAL score 0.8), intermediate-risk (SOKAL score 0.8 to 1.2), and high-risk (SOKAL score >1.2) patients are categorized. In this study, there was highly statistically significant difference as regard SOKAL score in studied groups and MMR. Patients with high SOKAL score starting on imatinib failed to achieve early MMR in comparison to low and intermediate SOKAL score. In groups 2 and 3 with high SOKAL score, patients achieved early MMR similar to low and intermediate risk. This was agreed with what observed by Saglio, et al. [11] among patients with a high SOKAL risk, rates of major molecular response at 12 months were higher for patients receiving 300 mg of nilotinib than the group receiving imatinib. Rates of major molecular response were also higher for nilotinib as compared with imatinib, at 3, 6, and 9 months. Also this was consistent with Larson, et al. [8], where rates of MMR were significantly higher for nilotinib low, intermediate and high SOKAL risk groups compared with imatinib. Hughes, et al.[12] stated that Patients with high SOKAL risk scores were much more likely to achieve MMR on nilotinib than imatinib, with MMR failure observed in more than half patients with high SOKAL risk scores in the imatinib group. Rates of MMR failure were also lower on nilotinib than imatinib among patients with low and intermediate SOKAL risk scores. A similar results observed by Saglio, et al. [11], among patients with a high SOKAL risk, where rates of major molecular response at 12 months were 41% for patients receiving 300 mg of nilotinib, and 17% for group of patients receiving imatinib. Hochhaus et al. [13] also stated that overall and within each SOKAL risk group, more patients achieved MMR 4.5 with nilotinib *vs.* imatinib.

In our study, there was statistically significant difference on comparing CCR with different groups at period of 6 and 12 months after start of treating patients. In group 2 and 3 started on nilotinib 300 mg, patients achieved CCR at 6 and 12

months more than group 1 patients starting on imatinib had lower response. This agreed with Saglio, et al. [11] where by 12 and 6 months, rates of complete cytogenetic response were significantly higher among patients receiving 300 mg of nilotinib (80%) as compared with those receiving imatinib (65%) (P<0.001) for both group. In our study, there was statistically significant difference between studied groups as regard ECG changes. In group 2 and 3, patients on nilotinib had ECG changes in form of QT prolongation. Similar results reported by Larson et al. [8] the incidence of IHD was higher on nilotinib than on imatinib. Also Hochhaus, et al. [13], reported that cardiovascular events were frequent with nilotinib more than imatinib, especially in the nilotinib 400 mg twice. However, Hochhaus, et al. [13] reported that symptomatic QT prolongation was infrequent.

In our study, there was statistically significant rise in liver enzymes in groups 2 and 3 where patients on nilotinib (300 mg) had elevated liver enzymes in comparison to their initial results. In group 1 where patients on imatinib 400 mg had no elevating liver enzyme in comparison to their initial results. Similar results reported by Saglio, et al. [11] where elevations of any grade in levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin were more frequently observed in both nilotinib groups than in the imatinib group. However Cortes, et al. [14], reported that laboratory abnormalities were uncommon in the nilotinib and included elevated levels of, alanine aminotransferase, aspartate aminotransferase, and total bilirubin. Also Hochhaus, et al. [13] stated that indirect hyperbilirubinemia was self-limited and reversed spontaneously with continued nilotinib therapy at the same dose.

In our study, there is statistically significant difference between studied groups as regard to Early Molecular Response (EMR) at 3 months in group 2 and 3, where patients on nilotinib 300 mg had achieved EMR in comparison group 1 in which patients on imatinib had EMR failure. This was a similarly by Hochhaus, et al. [13] where rates of EMR and *BCR-ABL* IS ≤ 1% at 3 months were higher in the nilotinib *vs*. those on imatinib who had BCRABL IS>1% to ≤ 10% at 3 months suggests that early and deeper levels of molecular response may provide additional long-term benefits. This also consistent with Hughes, et al. [12]. Observations where more patients achieved *BCR-ABLIS* <10% and BCR-ABLIS <1% at 3 months on nilotinib than on imatinib (P<0.001), Patients on imatinib had higher rates of EMR failure than those on nilotinib across all 3 SOKAL risk score groups. Similar results reported by Milojkovic, et al. [15] where after 3 months of second line therapy, patients had a BCR-ABL1/ABL1 ratio <10% [16].

CONCLUSION

In our study there was highly statistically significant difference between studied groups as regard MMR at 12 Month in group 2 and 3 where patients on nilotinib 300 mg where they had MMR than group 1 in which patients were on imatinib. This was consistent with what stated by Saglio where at 12 months, the rates of major molecular response for nilotinib 300 mg were nearly twice that for imatinib (22%) (P<0.001 for both comparisons). In our study, there was statistically significant difference between additional cytogenetic abnormalities and MMR as patients with additional cytogenetic abnormalities starting on imatinib had lower number of patients achieved MMR. This was consistent with Marin observation where additional cytogenetic abnormalities in Ph clones both at diagnosis and during follow-up of patients starting on imatinib are associated with poor outcomes. Treatment with first line nilotinib has a better clinical outcome than starting with imatinib followed by switching to nilotinib for inadequate responses.

ETHICAL APPROVAL

Approval was obtained from Ain Shams University Academic and Ethical Committee. Also an informed consent to participate and publish was obtained.

COMPETING INTERESTS

No interests of a financial or personal nature.

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AUTHOR CONTRIBUTION

Authors contribute equally in the study.

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