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ORIGINAL ARTICLE

Treatment Responses in Patients with Chronic Myeloid Leukemia on Tyrosine Kinase Inhibitors (TKI) Therapy

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is a cancer of white blood cells results by the BCR-ABL translocation. Part of BCR gene from chromosome 22 is fused with ABL gene on chromosome 9.
Aim: To observe percentage of patients achieving Cytogenetics response (CR), and Deep molecular response (DMR) in CML patients taking TKI (Imatinib and Nilotinib).
Study Design: Retrospective Cohort study.
Methodology: This study was conducted in 2018-2019 in about 198 CML patients to evaluate TKI therapy response and observation was based upon their Quantitative PCR test which gave percentage of BCR-ABL gene translocation in IU. Patients which were diagnosed with CML in 2016 and was regular in their treatment for about 2 years were included in the study. No intervention was given as in vivo study. **Statistical analysis:** Data analyzed by SPSS 25.0v.
Results: Results showed that out of 198 CML patients, started on 1st line TKI (imatinib) 95 males (48%) and 103 females (52%) showed cytogenetic response at start of therapy and after 2 years of therapy 157 (79.3%) patient showed DMR.
Conclusion: This study concluded that regular 2-year treatment of chronic CML patients with TKIs produced significant response in patients.
Keywords: BCR-ABL Translocation, Cytogenetic Response, Major Molecular Response, Complete Molecular Response and Deep Molecular Response.

INTRODUCTION

Cancer is one of the challenging conditions in medical sciences. Its complexity makes it difficult to treat. Among cancer types acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL) are most prevalent[1]. New emerging types of cancers cause serious threats to quality of life and survival of the humans. At present chronic myeloid leukemia (CML), a type of blood cancer is not completely defined that make its treatment difficult. So, studies are conducted to evaluate the effectiveness of suggested treatment regimen i.e. tyrosine kinase inhibitors (TKIs) in CML. Chronic myeloid leukemia (Chronic myelogenous leukemia or Philadelphia chromosome) is uncontrolled proliferation of WBCs, on chromosome no 9 and 22 their genes BCR-ABL translocate which triggers process of abnormal WBCs production. Part of BCR gene from chromosome 22 is fused with ABL gene on chromosome 9. ABL carries a domain that can add phosphate groups to tyrosine residues (a tyrosine kinase). BCR-ABL fusion gene product is also a tyrosine kinase. TKI inhibits addition of phosphate to tyrosine residues (inhibit phosphorylation). It usually occurs in middle ages and in elderly[2].

Clinical symptoms indicating the occurrence of CML include splenomegaly, fever, tiredness, early satiety, night sweat, pale skin and shortness of breath, bruising and bleeding[3]. Old age and male gender are non-modifiable increase the risk of CML incidence. Radiation exposure is modifiable risk factor to develop CML. Family history is not a risk factor for CML as its not a hereditary disease. For diagnostic purposes ultrasound, CBC and PCR (polymerase chain reaction) can be done.

The study conducted by Stephane Picard, showed that the monitoring of imatinib plasma levels is useful for the management of CML patients[4]. The study conducted by Asif khalid, Maliha Zahid in 1994 concluded that CML is more common as compared to chronic lymphocytic leukemia and occurrence of CML is more common in young people[5]. A study conducted by Saad Z Usmani, concluded that the advent of Tyrosine Kinase Inhibitors will have more impact on lifespan of CML patient in Pakistan when compared with patients in western hemisphere due to younger age at diagnosis[2]. In October 2006 Timothy Hughes, worked to harmonize different methodologies for measuring BCR-ABL genes[6]. Nighat Naseem in 2013 conducted study on male and female population determining the prevalence of leukemia[7]. Brian J. Druker, M.D, Francois Guilhot conducted states that after 5-year follow up treatment with imatinib induce durable effects in CML patients[8]. Andreas hochhaus stated that even after the 11 years of follow up with imatinib its efficacy persisted and no unacceptable toxic effects appeared[9]. A study by Claude Preudhomme in 2010 evaluate the effectiveness of imatinib in CML patients when given in combination with peginterferon alfa[10]. Charles L. Sawyers in 2010 studied that CML patients which are interferon resistant imatinib quickly become a standard treatment because of drug marked efficacy and minimal toxicity[11]. In 2009 Elias Jabbour conducted a study focusing the suboptimal response and failure causes of treatment with imatinib in CML patients[12]. In November 2010 proff. Francois evaluate the effects and consequences of discontinuation of imatinib in patients who have achieved a complete molecular response[13].

This study was conducted to evaluate TKI therapy responses in CML patients. Treatment responses in CML patients on TKI therapy are not being evaluated in Pakistan yet so this study had provided important information regarding treatment responses, optimum response duration.

The objective of the study was to observe percentage of patients achieving Cytogenetics response (CR), and Deep molecular response (DMR) in CML patients taking TKI (Imatinib and Nilotinib).

METHODOLOGY

This study was (retrospective cohort study conducted in Vivo) conducted at Oncology department Allied Hospital Faisalabad. Study was started after ethical approval. In this study no

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intervention was offered regarding treatment. It was a retrospective study. Data was collected from patients record file which were on TKI therapy (1st and 2nd generation). To be included in this study only those patients were considered (inclusion criteria) who were diagnosed with CML in 2016. Also, those patients who were regular in their follow-up visits and were punctual with their prescribed therapy. Besides this those patients who were not regular in their follow-up visits in hospital or not taking the medication regularly and those who were not adhered to therapy were excluded from the study. Purposive convenient sampling technique was used to collect the data, using Sample size of 198 subjects.

Statistical analysis: The data was summarized and analyzed on Statistical package for social sciences (SPSS) version 25.0. Data was collected by the pre-designed data collection form. Including Demographics and laboratory reports (Monthly CBC an BCR-ABL quantification PCR after 6 months).

RESULTS

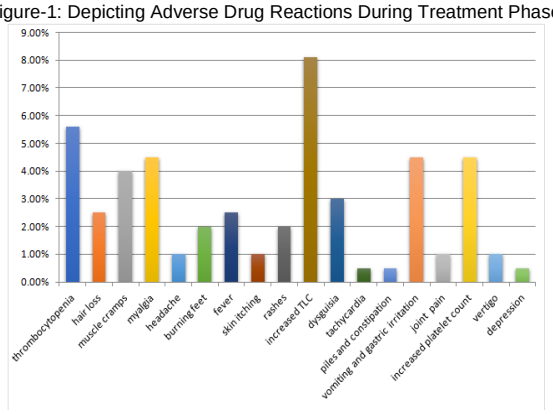
On examining the demographic parameters of the included patients results showed that total of 198 CML patients on TKI therapy were included in study their age was 45.17±13.542. Among them 86.9% were in adult population and population was equally distributed among male and female patients. 36.4% of patients were on 5th year of TKI therapy. Majority of population was from Faisalabad 47% rest 53% were distributed from various cities of Western Punjab. disease stages and their frequencies were tabulated as table-1. \

Table-1:Disease Stages with their frequency

CML-Chronic phase	1st line=91 (46%)
CML-Resistant to Imatinib	Accelerated Phase=32 (16.2%)
CML-Resistant to imatinib	Chronic phase=25 (12.6%)
CML-Chronic phase	2nd line=7 (3.5%)
CML-Intolerant to imatinib	Chronic phase=39 (19.7%)
CML-Intolerant to imatinib	Accelerated phase=1 (0.5%)
CML-Accelerated phase	1st line=3 (1.5%)

Adverse drug reactions (ADRs) were expressed as figure-1. Frequency and type of ADRs in 1st line therapy did differ from the 2nd line TKI therapy patients as tachycardia and depression were observed only in patients on 1st line therapy and frequency of thrombocytopenia and vomiting and gastric irritation.

Figure-1: Depicting Adverse Drug Reactions During Treatment Phase



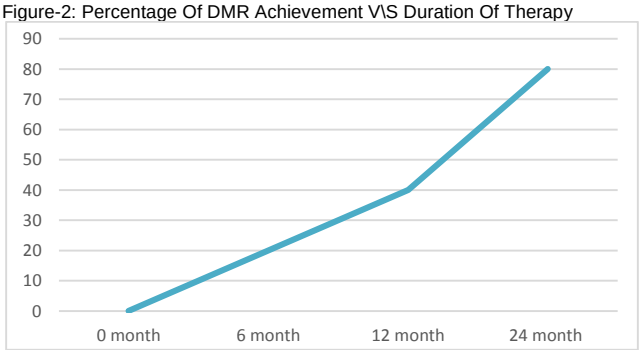
ADRs as vertigo, headache, piles and constipation were only observed in CML patients on 2nd line TKI therapy while increased TLC and hair loss was most frequently observed in such patients. Details of the drug shifting in CML patients were summarized in table-2.

Regarding the percentage of response achieved (figure-2) at start of therapy (0mon) average BCR-ABL translocation was 44.33±25. 93% no patient had achieved DMR. After 6mon of therapy average BCR-ABL translocation was 8.54±15. 98% and 17.7% of CML patients achieved DMR while MMR and EMR was also observed and CR still restrained in 14.1% patients. After 24 months of TKI therapy mean value of BCR_ABL translocation in CML patients was 0.019±0.022%. DMR was achieved in 79.3% of patient population CR was diminished after 24 months of therapy in all of patient population while MMR and EMR was still observed in patients (figure-2).

Table-2: Drug Shifting In CML Patients

Register Drug/Line of Drug	Imatinib (1st line) =110 (55.6%)
	Nilotinib (2nd line) =88 (44.4%)
Current drug/ line of drug	Imatinib (1st line) =96 (48.5%)
	Nilotinib (2nd line) =102 (51.5%)
Drug Shifting	Not Shifted=176 (88.9%)
	From 1st line to 2nd line=18 (9.1%)
	From 2nd line to 1st line=4 (2%)
Mean drug shifting time = 3.5 months	

Figure-2: Percentage Of DMR Achievement V\S Duration Of Therapy



DISCUSSION

The findings of current study showed that CML prevalence is higher in adults. This finding of the study are comparable to other studies[2,4] conducted which gave that the prevalence of CML is higher in median age group i.e. adults. In current study it is found that after the 12month of therapy with 1st line TKI therapy Imatinib 23(11.6%) of CML patients achieved MMR while in another study[4], it is found that on 12 month of TKI therapy MMR is achieved in 50% patients. According to findings of current study there are 32(16.2%) CML patients are in or being shifted to accelerated phase while in another study[4], there are 18(52.9%) patients shifted to accelerated phase. The difference in study results is due to a large difference in the numbers of study population and the inclusion criteria of the study being discussed in which patients which were on the blast crisis were included in the study. In this study 110(55.6%) patient registered on 1st line TKI therapy imatinib and continued in 96(48.5%) patients while in another study[8], TKI 1st line therapy imatinib continued in 69% patients and also in our study 18 (9.1%) patients shifted from 1st line TKI therapy to 2nd line TKI therapy while in other study only 3% patients were shifted from 1st line TKI to 2nd line. In current study it is found that after the 6 months of therapy with Imatinib cytogenetic response was observed in 28 (14.1%) patients and major molecular response was achieved in 36 (18.2%) patients while according to another study[3] cytogenetic response achieved in 37.5% patients and major molecular response was achieved in 60.2% patients at 6 month therapy with imatinib. And at 18 months of therapy with imatinib cytogenetic response was achieved in 29 (14.6%) patients and major molecular response was achieved in 23 (11.6%) patients while in comparison to population after 12 month of TKI therapy in the same study it was found that cytogenetic response was achieved in 58% patients and major molecular response was achieved in 70% .

In this study there were 40(20%) patients were intolerant to imatinib 1st line TKI therapy while in comparison to another study[8], 4 (<1) patients were intolerant to imatinib. The greater occurrence

of intolerance was due to patient non-compliance to the therapy, improper dosing regimen. In this study the incidence of ADRs with imatinib 1st line TKI therapy was found to be in 35 (36.5%) patients while in another study[9], this percentage was only 4% i.e. in 23 patients out of 533. The reason of low ADRs was due to the high number of the individuals being included in the study and the patients were in controlled conditions i.e. they were clearly following the instructed dosing of drug and follow up period of the discussed study was up to 60 months and that population most of ADRs diminished over this period of the treatment.

According to the results of this study by use of 1st line TKI there was increased TLC levels in 4(4.2%) were observed while another article[8], this increase in TLC was observed in only 2(<1%) patients by use of imatinib 1st line TKI. In our study increase TLC was found in 4(4.2%) by use of imatinib 1st line TKI therapy and 12(11.8%) patients had increased TLC by use of 2nd line TKI therapy nilotinib. While another study[12], showed that by use of 1st line TKI imatinib there was increased TLC in 82% population and 73% patients had increased TLC by use of 2nd line TKI therapy.

Our study showed that with the use of imatinib 1st line TKI there were increased platelet count in about 4 (4.2%) patients and 5(4.9%) had increased platelet count by use of 2nd line TKI therapy while another study[12], showed that by use of imatinib 1st line TKI there were increased platelet count in about 31.8% patients while by use of 2nd line TKI therapy there were increased platelet count in 28% patients. Our study showed that there was achievement of deep molecular response in 35(17.5%) patients after the 6 month of therapy and after the 18 month of therapy deep molecular response was achieved in 81(40.9%) patients while the other study[12], there was achievement of deep molecular response in about 53% patients after 6 month of therapy and 66% patients achieved deep molecular response after 12 month of therapy.

In our study the 2 years of follow up DMR rate in 96 CML patients treated with Imatinib was 77(80.2%). In a separate study performed in the United Kingdom, the 5-year cumulative MMR rate in 204 chronic phase CML patients treated with imatinib was 50.1%[5]. In our study after 2 years of follow-up 9.1% of CML patients treated with imatinib are not receiving their initial therapy and drug shifting occurred in them reason behind included disease progression and intolerance to the therapy. In another study after 5 years of follow-up in the DASISION trial (in the final report), 37% of those treated with imatinib are no longer receiving their initial therapy[3]. The difference in the results is due to the extended follow up of the patients in the study compared with.

In our study after 2 years of follow-up 2% of CML patients among patients treated with nilotinib are no longer receiving nilotinib. In another study the 5-year follow-up of the CML patients on the TKI therapy showed that 40% of patients treated with nilotinib 300 mg twice per day and ,38% of those treated with 400mg twice per day had discontinued therapy[9]. In both studies the drug shifting from their front-line therapy occurred. The difference in percentage of drug shifting in both studies may be due to difference in the sample size. In our study 48.5% patients are on imatinib and 51.5% patients are on nilotinib. Among the patients on imatinib 80.2% patients achieved DMR and among patients treated with nilotinib 78.4%patients achieved DMR. We compare responses of both imatinib and nilotinib statistically as initial therapy and found no statistical difference (p value 0.78). Another study demonstrated that Dasatinib, nilotinib and high-dose imatinib elicit very similar treatment responses in patients treated first-line with these tyrosine kinase inhibitors[3]. In another study 321 patients included in this analysis, 70% were imatinib resistant and 30% were imatinib intolerant. The 24-month follow-up results showed that treating them with nilotinib is effective as 59% of patients achieved mcyr and 44% of patients achieved ccyr[13]. Patients shifted from first line to second line = 18. Similar is the case with our study population in which drug shifting from 1st line to 2nd line was 9.1% and after drug shifting significant patients achieved desired DMR.

Limitations: Our limitations included time with financial constrains and limited resources. No genetic workup was done for enrolled subjects.

CONCLUSION

This study concluded that Regular 2-year treatment of chronic CML patients with TKIs produced significant response in patients. However, in case of resistance 1st line treatment can be shifted towards the 2nd line. But if response is not achieved it could lead to the ALL (acute leucocyte leukemia) which have deadly consequences.

Author's contribution: AAM&ARM: Conceptualized the study, analyzed the data, and formulated the initial draft, **UR&IS:** Contributed to the histomorphological evaluation, **FA&MK:** Contributed to the analysis of data and proofread the draft, **THM:** Contributed to data collection, **TL:** Contributed to the proofreading the manuscript for intellectual content,

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