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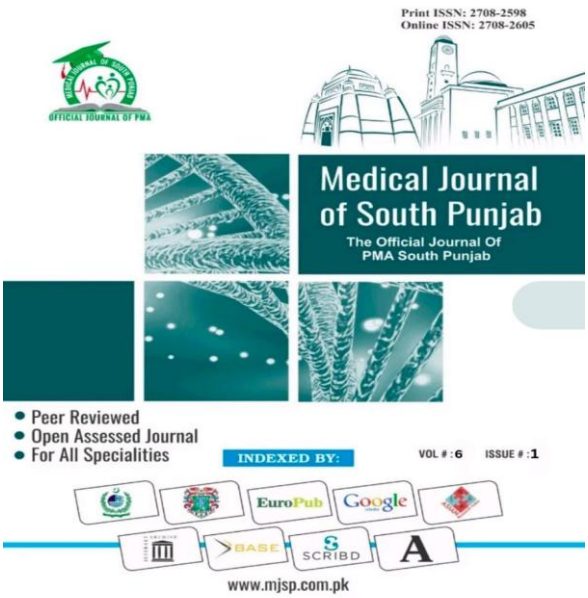

Frequency of molecular response in a patient of chronic myeloid leukemia taking Tyrosine Kinase Inhibitors after 1 year of treatment Pakistan Institute of Medical Sciences experience

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ABSTRACT

Objective: To determine frequency of major molecular response in a patient of CML taking TKIs after 1 year of treatment PIMS experience.

Methods: Current study included 121 patients by nonprobability consecutive sampling technique. Patients who didn't follow up regularly and refused to participate in the study were excluded. After taking consent,age, gender and residential status were documented. Venous blood sample (3cc) was drawn and sent to the laboratory for the quantification of BCR-ABLI through mRNA GeneXpert to determine the major molecular response. Data was analyzed by SPSS 27. Descriptive statistics were applied for the age of patients to calculate mean and S.D. Frequencies were calculated for gender, age groups, residential status, and major molecular response. P value ≤ 0.05 was labelled significant.

Results: Mean age of the patients was 44.21±11.64 years; and 73(60.3 %) were males and 48(39.7 %) were females. MMR was seen in 43.0% of the patients.MMR was seen in 34.5% of the patients in 18-35 years-group; in28.9 % of 36-50 years-group; and in61.7%of 51-60 years-group(p=0.004).

Conclusion: TKIs have proven to be effective treatment choices for patients of CML, especially in older age groups.

Keywords: Major molecular response (MMR),chronic myeloid leukemia (CML), tyrosine kinase inhibitors (TKIs).

1. INTRODUCTION

Chronic Myeloid Leukemia (CML) is a myeloproliferative cancerand theassessed incidence is 1-2 per 100,000 adults, globally.[1]Translocation between BCR and ABL genes in chromosome 22 and 9, respectively, is the root cause of CML. This translocation gives rise to Philadelphia chromosome (t:9;22) leading to the production of BCR-ABL protein. BCR-ABL protein is linked to kinase activity which causes unrestrained proliferation of hematopoietic stem cells.

With the emergence of Tyrosine Kinase Inhibitors (TKI), the treatment of CML has significantly transformed.TKIs interfere with the interface between Adenosine Triphosphate (ATP) and on coprotein BCR-ABL, and therefore, inhibit the neoplastic cellular propagation [2].The primary use of TKIs as the primary therapy for chronic myeloid leukemia (CML) is due to their high efficacy. TKIs have achieved an overall survival rate exceeding 90%[3]. The current treatment objective for CML focuses on ensuring long-term survival with a good quality of life. This includes achieving a constant deep molecular response (DMR) and enabling treatment-free remission (TFR).[3]

The prognosis for patients of CML has improved significantly over the past two decades, largely due to the introduction of five small-molecule TKIs—Imatinib, Nilotinib, Bosutinib, Dasatinib, and Ponatinib—as first- or second-line therapies[4–5]. The clinical benefits of TKI therapy for CML are well-established, including the ability to achieve deep molecular responses, prevent disease progression, and restore life expectancy to near-normal levels[6–7]. However, treatment complications must be carefully managed following the European Leukemia Net (ELN) recommendations. These guidelines emphasize monitoring molecular responses at three, six, and twelve months, classifying patient responses as optimal, warning, or failure[8].

Kizaki et al conducted an observational study to assess the efficacy of TKIs in recently diagnosed patients with CML-chronic phase (CML-CP). Results of his study showed that an early molecular response (EMR) at 3 months BCR-ABL1 <10% was detected in 328 (87%) of 377 patients and 39.6% MMR were reported at 12 months[9]. While another study reported lower results i.e., 19% MMRs based on BCR-ABL data in 12-18 months following therapy[2].

Different studies done in different parts of the world have reported variable results but there is no such data available for local population. Although, TKIshave proven to be effective as assessed by the hematologic response, there is a significantly high rate ofpoor response and high resistance rate. Steady monitoring of the CML patients is required in order to identify resistance to TKIs so that alternative management options can be implemented to improve the results. During CML therapy, resistance mechanisms need to be explored in order to adjust the use of various TKIs, as a single regimen or in various combinations. So, we have planned to conduct this study in local population of Islamabad and the observations of this study will help clinicians to diagnose early and proper management accordingly which will help in improving the quality of life of our patients.

2. METHODOLOGY

This is a prospective observational study conducted at OPD of Medical Oncology Department, Pakistan Institute of Medical Sciences (PIMS) Islamabad, from May 2024 to November 2024.Approval was taken from Institutional Ethical CommitteeA study by Sumantri et al.[2] was taken as reference and sample size was calculated taking frequency of MMR i.e.,19% with 7% margin of error and 95% confidence level. Current study included 121 patients by nonprobability consecutive sampling

technique. All the patients of both male and female gender, 18-60 years of age, diagnosed with chronic myeloid leukemia and were taking TKIs like Imatinib or Nilotinib as treatment were included in the study. Chronic myeloid leukemia was labelled when BCR-ABL1 fusion gene came positive on FISH or PCR, with raised TLC (>11,000/µl), bimodal peak of myelocytes and segmented neutrophils, normal or raised platelet count on CBC examination, hypercellular marrow with normal or slightly left shifted myeloid maturation, and no significant dysplasia with or without blasts accounting for < 5% of marrow cells. Patients who didn't follow up regularly and refused to participate in the study were excluded.

Informed consent was obtained from every patient after proper explanation of the procedure and purpose of the study, and ensuring the confidentiality of the information provided by the patient. Age, gender and residential status were documented. Venous blood sample (3cc) wastaken for the quantification of BCR-ABLI through mRNA GeneXpert to determine the MMR. MMR was labelled on the basis of GENE XPERT report as >3-log reduction of BCR-ABL1 transcript [BCR-ABL1 international scale (IS) ≤ 0.1%]. All the findings were recorded on a proforma, by the researcher.

Data was analyzed by using SPSS version27. Descriptive statistics were applied and mean and standard deviation were calculated for the age of patients. Frequencies and percentages were calculated for nominal data like gender, age groups, residential status, and MMR. Effect modifiers like gender, age groups and residential status were controlled by stratification and post stratification chi-square test was applied to see their effect onMMR. Pvalue ≤ 0.05 waslabelled as significant.

3. RESULTS

Total 121 patients were enrolled in the study. Study group included patients of 44.21 ± 11.64 years and 73 (60.3 %) were males and 48 (39.7 %) were females. Of all the patients, 72 (59.5 %) were resident of urban area while 49 (40.5 %) were residents of rural areas. MMR was seen in 52 (43.0 %) of the patients.Table-I

Table:I Demographicdata and MMR

Variable	Value (n=121)
Age, years	44.21±11.64
Gender, N (%)	
Male	73 (60.3 %)
Female	48 (39.7%)
Residential status, N (%)	
Urban	72 (59.5 %)
Rural	49 (40.5 %)
MMR, N (%)	
Yes	52 (43.0 %)
No	69 (57.0 %)

Data is entered as mean ± S.D. unless mentioned otherwise.

Table-II: Assessment of MMR after stratification of data

Effect modifier	Subgroup	MMR	P value
Age, years	18-35 (N=29)	10 (34.5 %)	0.004
	36-50 (N=45)	13 (28.9 %)	
	51-60 (N=47)	29 (61.7%)	
Gender	Male (N=73)	29 (39.7%)	0.373
	Female (N = 48)	23 (47.9%)	
Residence	Urban (N=72)	28 (38.9 %)	0.271
	Rural (N=49)	24 (49.0 %)	

Patients were divided on the basis of ae groups i.e., 18-35 years of age group included 29 patients; 36-50 years age group included 45 patients; 51-60 years age group included 47 patients. MMR was seen in 10 (34.5 %) of the patients in 18-35 years' age group; in 13 (28.9 %) of the patients in 36-50 years age group; and in 29 (61.7%)of the patients in 51-60 years age group. The observed difference was of statistical significance (p=0.004). MMR was seen in 29 (39.7%) of the males and in 23 (47.9%) of the females (p=0.373). MMR was seen in 28 (38.9 %)of the patients from urban area and in 24 (49.0 %) of the patients from rural areas (p=0.271). Table-II.

4. DISCUSSION

Imatinib has emerged to be the first line treatment for newly diagnosed patients of CML. However, approximately one-third of patients experience a suboptimal response to imatinib, either due to primary failure or progression after an early response [10]. Treatment resistance can arise from various mechanisms, including point mutation in the BCR-ABL, which result in reduced efficiency and poorer results[11]. Escalating the dose of imatinib to 600 mg or 800 mg daily has proven effective for patients with poor responses or disease progression [12]. At a center in Iraq, over 86% of patients with disease progression received an escalated dose of imatinib before transitioning to second-line TKIs[13].

Current study observed MMR in 43% of the patients. The response rate was higher among the patients of older age group, i.e., 51-60 years. In a study by Mjali A et al.[13], nilotinib therapy was given without the analysis of mutations due to the unavailability of the screening test for poor response or failure of imatinib treatment. They observed that 66.67% of the patients achieved MMR, which was higher than the 58% and 57% reported in Latin America and Asia, respectively [11,14]. The BCR-ABL transcription levels significantly reduced at 3, 6, and 12 months, consistent with findings by Yeung et al., where MMR improved over time [15].

MjaliA et al.[13] observed that better survival among males than among females. Similar findings were observed by other researchers as well[16,17]. However, current study found out no statistically significant difference in MMR among different genders.

Haque A et al. [18] observed MMR in 36% patients using imatinib and in 52% using nilotinib, after 9-12 months of treatment.Their observed results were close to those observed in current study. Singh R et al. observed MMR in 71.5% of the patients takingnilotinib. In another study [20], MMR was 72.7%and 53.5% with Imatinib and Nilotinib, respectively.

5. CONCLUSION

TKIs are effective treatment options for patients of CML. Especially the older age groups show MMR after being treated with TKIs for CML for a minimum period of one year.

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