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ORIGINAL ARTICLE

Imatinib resistance in CML and its association with age & gender.

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ABSTRACT… Objective: To evaluate the association of gender and age with the resistance shown to Imatinib in CML with evaluation of WBCC in different age groups. **Study Design:** Cross Sectional Analytical study. **Setting:** Islamic International Medical College, Riphah International University, Islamabad, Pakistan. Patients were enrolled from the CML clinic in Holy Family Hospital, Rawalpindi. **Period:** January 2019 to December 2021. **Material & Methods:** Sampling technique was non probability consecutive sampling. We included 75 newly diagnosed CML patients, who were taking Imatinib 400 mg. Blood samples of all these patients were analysed at the start of treatment and also after 3 months to determine the complete haematological response (CHR) and patients were labelled as resistant who failed to achieve complete haematological response at this stage according to the Leukemia Net guidelines. **Results:** Our study demonstrates that 54.7% of the patients were Imatinib responders while 45.3 % patients were Imatinib resistant. Patients who were labelled as responders have shown complete haematological remission at 3 months of treatment. (Platelet Count < 450 x 10 9/L - WBCC < 10 x 10 9/L - Differential without Immature Granulocytes (MC, PMC, MB) and With Less Than 5% Basophils - Non-Palpable Spleen) A chi square test of independence was performed to examine the relation between gender and response and between age groups and response. The relationship between age groups and response is significant with p value of 0.003. While the relationship when determined between gender and response, it was found to be non-significant with p value of 0.08. It was also found out that WBC count in responders is at lowest in second age group and also highest in second age group in case of resistant patients that is age between 31-40 years. **Conclusion:** Imatinib resistance is common while treating patients with chronic myeloid leukemia. There is significant association with the different age groups and non-significant association with the gender in terms of response to the treatment of Imatinib. It was also found that age also effects the WBC count with Imatinib though it was not significant.

Key words: Chronic Myeloid Leukaemia, Complete Haematological Response, White Blood Cells, White Blood Cells Count.

INTRODUCTION

Ethnic and geographic differences does not influence much on the annual incidence of chronic myeloid leukaemia which is around 10-15 cases /100,000.[1] A study conducted in Pakistan showed CML as the second commonest leukemia type putting a substantial burden on health needs of the country. Bone marrow transplantation with frequent adverse events and considerable mortality was the only option as sustained remission could not be achieved with drugs around ten years ago.[2] Chronic myloid leukemia is the acquired mutation of bone marrow stem cells which can lead to myeloproliferative disorders. Fusion of BCR and ABL 1 genes by reciprocal translocation of t(9;22)(q34;q11) of chromosome 9 & 22 is the known cause of this malignancy as this fusion results in enhanced activity of baseline active tyrosine kinase BCR-ABL protein.[3,4] This derestricted tyrosine kinase activity has been shown to be essential and enough for the malformed picture of cells in CML.

In the recent advances of cancer chemotherapy, CML is of main focus because of the recognized target of deranged kinase activity of Bcr-Abl protein product. This had led to the development of tyrosine kinase inhibitors (TKIs).[5,6] After recognizing the causal molecular defect, rational drug was designed successfully for the ultimate

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cure of CML and Imatinib was introduced after approval from the regulatory authorities. It is a 2-phenylaminopyridine derivative that is effective for the management of all phases of CML. Function of tyrosine kinase expressed by Bcr-Abl is blocked by it. First line of treatment for all leukemias with increase expression of aberrant Bcr-Abl kinase is Imatinib.[7,8] Though the initial success is achieved with reversal of disease parameters, long term remission of CML with Imatinib is an intimidating problem and there is development of resistance in considerable number of patient over prolonged use. Development of resistance occurs in most of CML patients with blast or accelerated phase (late stage) and a few with chronic phase. This raises concerns with Imatinib administration as disease progression could not be halted effectively.[9]

Imatinib resistance may have association with age and gender.[10 ,11] Guidance can be sorted out if treating physician has baseline information regarding association of resistance with these two important demographic features of newly diagnosed CML patients as it will save their time to switch to second generation tyrosine kinase inhibitors that is Nilotinib and Dasatinib as they had shown better clinical activity against different types of mutations both in vivo and in vitro.[12]

This exploratory study is designed to predict potential association of Imatinib resistance with gender and different age groups in newly identified chronic myeloid Leukemia patients and also impact of age on WBC count in responders and resistant patients.

MATERIAL & METHODS

In the department of Pharmacology and therapeutics, Islamic International medical college, this cross sectional analytical study was carried out with the formal approval from ethical review committee of Institution (Ripah/ ERC/18/0287) from January 2019 to Dec 2021. There was no conflict of the study with the Declaration of Helsinki and Good clinical practice. Patients were included from the CML clinic in Holy Family Hospital, Rawalpindi. 75 Chronic myeloid leukemia patients between age 18 and 70 years were enrolled in the study after informed written consent. Inclusion criteria was newly diagnosed patients who are taking Imatinib 400mg and do not have any other comorbidity and showing good compliance towards treatment.

Sampling technique was non probability consecutive sampling. Sample size of 100 patients was selected according to the reference studies[13] but later on due to drop outs or unable to follow up, it was reduced to 75 patients. They were followed on the basis of leukaemia net guidelines.[14] One group was showing good clinical response to Imatinib initially then after 3 months, complete haematological response (CHR) could not be achieved.[15] This group was considered as the group which could not sustain remission. While the second group showed the good haematological response at the end of three months. First group was taken as resistant group and second group was taken as responders. The group with good haematological response was further followed up for next three months for possibility of development of resistance during the course of treatment as it is not very uncommon. During this period their monthly complete blood test were taken and that showed good haematological and clinical response.

Data analysis Procedure

Microsoft SPSS-23 was used for the statistical analysis of data. Descriptive statistics was used with the mean ± SEM in groups. Chisquare was employed to compare categorical variables and determine association of different age groups and gender with the response to the treatment of Imatinib. One-way ANOVA and post hoc tukey test was applied to compare changes in WBC levels of multiple age groups as it is the main determinant to define the complete Hematological response according to the Leukemia net guidelines. P values less than 0.05 was considered significant.

RESULTS

After applying inclusion and exclusion criteria, 75 patients with CML were enrolled in the study, out of them 41(54.7%) were responders while 34 (45.3%) were resistant. (Figure-1)

Leukaemia Net guidelines16 were followed to

define treatment failure and resistance patterns.

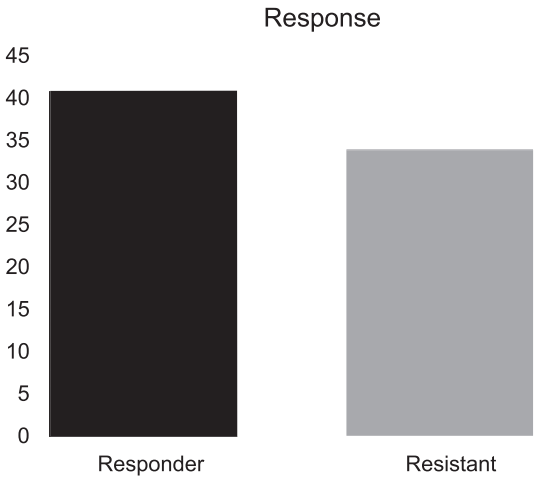

Figure-1. Responders & Resistant to the treatment of Imatinib

When responders were categorized on the basis of gender, 16 were males while 25 were females while in resistant group, 20 were males while 14 were females as shown in Table-I with their relative frequencies as well. A chi-square test of independence was performed to examine the relation between gender and response to Imatinib treatment and it was found out to be non-significant with p value of 0.08.

Relation of Age with Response to Imatinib:

On the basis of age, all the patients were divided into 4 groups[17] and Imatinib response status was assessed in each group. Relative frequencies of response whether responder or resistant are shown in Table-II. The mean age of responders was 39.75 ±1.76 years and resistant was 47.91±1.91 years. A chi-square test of independence was performed to examine the relation between all four age groups and ability to respond to Imatinib and it was found out to be significant with p value of 0.003 as shown in Table-III.

WBC status between responders and resistant was assessed and mean was found out to be 6.86±0.27 in responders while mean in resistant was 339.06±24.22. One-way ANOVA and post hoc tukey tests showed that there was non-significant difference in mean WBC count in different age groups of resistant patients with p value of 0.859. Though the p value in post hoc tukey test was not significant but it was found out to be better response in age group from 31-40 years in terms of reduction in WBC count in responders and similarly the same age group showed maximum increase in WBC count in resistant as shown in Figure-2 and Figure-3.

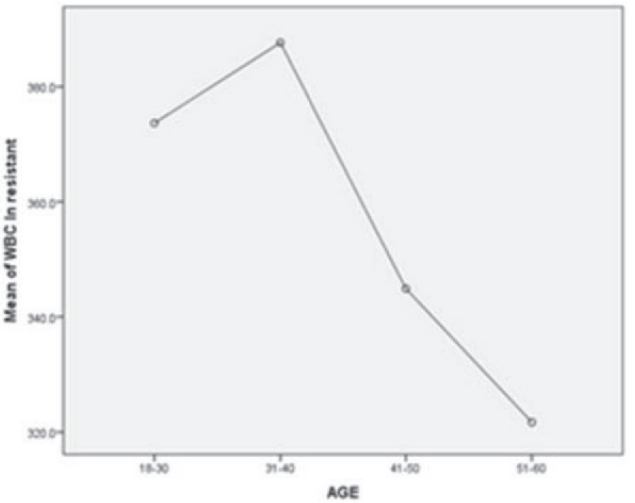

Figure-2. WBC in resistant

Gender		Response		Total
		Responder	Resistant	
Male	Count	16	20	36
	% Within Gender	44.4	55.6	100%
	% Within Response	39	59	48%
Female	Count	25	14	39
	% Within Gender	64	36	100%
	% Within Response	61	41	52%
Total	Count	41	34	75
	% of Total	54.7	45.3	100%

Table-I. Distribution of gender among responder and resistant

Age		Imatinib Response Status		Total
		Responder	Resistant	
Age 18-30	Count	11	3	14
	% Within age groups	78.6	27.4	100%
	% within response	26.8	8.8	18.7
Age 31-40	Count	6	3	9
	% Within age groups	66.7	33.3	100%
	% within response	14.6	8.8	13.3
Age 41-50	Count	19	11	30
	% Within age groups	63.3	36.7	100%
	% within response	46.3	32.4	38.7
Age above 50	Count	05	17	22
	% Within age groups	22.7	77.3	100%
	% within response	12.3	50	29.3
Total	Count	41	34	75
	% within response	54.7	45.3	100%

Table-II. Response status in different age groups

		Response		Total	P-Value
		Responder	Resistant		
Age	18-30	11	3	14	0.03
	31-40	6	3	9	
	41-50	19	11	30	
	Above 50	5	17	22	
Total		41	34	75	

Table-III. Chi square between all age groups

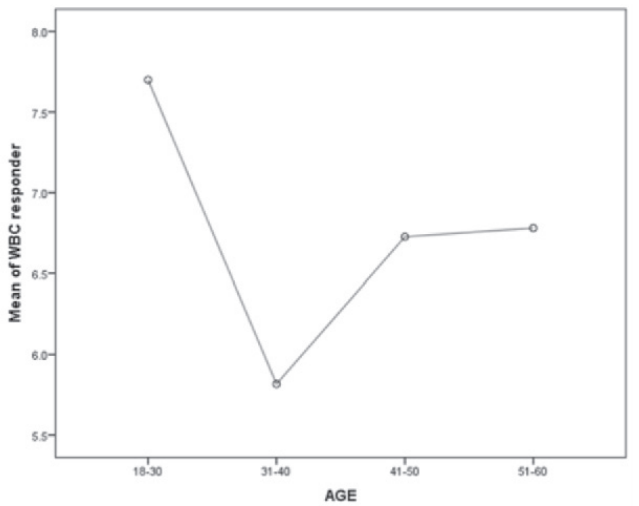

Figure-3. WBC in responders

DISCUSSION

Genetic and non-genetic influences are recognised factors for Imatinib resistance. Along with multiple genetic factors which are going to have an impact on the pharmacokinetics and pharmacodynamics of Imatinib, certain demographic features are also going to influence the response to the treatment.[18]

Achievement of complete haematological response is one of the main milestone in achievement of successful therapy with Imatinib in chronic myeloid leukemia which is the first line therapy offered to newly diagnosed patients. Therefore, according to the guidelines provided by leukemia net, these patients are monitored weekly for complete blood cell count and decision for achievement of complete haematological response is taken at 3 months as mentioned in study conducted by Attwood in 2021.[19] Assignment of study objects in two groups is in accordance with a similar study carried out by Ammar, M., Louati in 2020.[20] The WBC levels were significantly higher in resistant group as compared to the responders with significant p value of in our study (339.06±24.22 vs 6.86±0.27.). It was also found out that decrease in WBCC in the age group 2 is more marked as compared to other age groups though it was not significant but there is marked decrease in WBC count in responders similarly there was marked increase in WBC

count in resistant group. This finding was not in accordance with the study Specchia, G in 2021[10] which showed better response in sixties where other co morbidities are usually also present. According to this study Imatinib is preferably reserved for patients in fifties and above while newer TKIs are preferred in younger patients. Our study also showed the significant p value of 0.003 when different age groups were compared through chi square test and this parallels with the study of Belohlavkova, P in 2019[11] which also demonstrated that age might be one of the demographic feature which could affect the response of the Imatinib.

Current study had shown the significant relation of age with treatment response and the magnitude of association seemed different between different age groups with the maximum change in patients between 30 -41 years of age both in responder group and in treatment resistant group. Association with gender was also evaluated through chi square but it was not significant which means that gender might not influence the treatment pattern of leukaemia though this finding needs further exploration in our country with larger sample size. These results are in agreement with a population based study (n=32,638) of South European Region. They investigated gender and age based differences in Imatinib response in younger than 65 years.
It is recommended to consider diverse response modifying clinical factors when designing and evaluating chronic myeloid leukaemia patient treatment.

However, further studies are required to identify the effect of different genetic and demographic factors on pharmacokinetics, pharmacodynamics and adverse effects of Imatinib. This will improve the individualization of leukaemia treatment and contribute to better therapeutic outcomes with lesser disease burden.

CONCLUSION

The study revealed that resistance to Imatinib treatment is present in the selected cohort of patients. The resistance is associated with the age of CML patients. Though gender differences had not shown any influence on response but age has a positive association. This finding can help the treating physician to choose between first generation and second generation tyrosine kinase inhibitors though it may require further exploration with lager sample size from multiple centres.

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