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To Study Demographic Profile, Risk Stratification and Response to Treatment in Chronic Myeloid Leukemia Patients

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Abstract

Background

Chronic myeloid leukemia (CML) is most common leukaemia in India. The annual incidence of CML in India was originally reported to be 0.8 to 2.2 per 1,00,000 population. CML is a clonal disorder that is usually easily diagnosed by the Philadelphia chromosome. The approval of tyrosine kinase inhibitors has significantly reduced the mortality rate associated with CML and revolutionized treatment.

Material and Methods

80 diagnosed cases of CML were taken. Investigations were done and with EUTOS patients were stratified into low and high risk group and then treatment with Imatinib were given to all patients and molecular response was evaluated.

Results

In the study population, out of 80 patients in the study population 40 were females and 40 were males with M: F is 1:1. Out of total 80 patients' maximum patients (54) were in 31-60 years age group. Our study showed most common symptom of presentation is abdominal discomfort followed by fever. Out of total 80

patients, 25 (31.3%) patients had high EUTOS score and 55 (68.8%) patients had low EUTOS score. On 6 months follow up 36.3% patients had Complete Molecular Response, 16.3% patients had Major Molecular Response and 47.5% patients had No Molecular Response but on 12 months follow up 71.3% patients had Complete Molecular Response, 16.25% patients had Major Molecular Response and 12.5% patients had No Molecular Response.

Conclusion

In this study we found a significant correlation between EUTOS score and Molecular response at 6 months and 12 months follow up after Imatinib therapy.

Keywords

Chronic myeloid leukaemia, European Treatment and Outcome Study score, Response, Tyrosine kinase inhibitor.

Introduction

Chronic myeloid leukemia (CML) is most common leukaemia in India. There are no familial associations in CML. Almost half of those diagnosed with CML are usually asymptomatic and disease is often discovered during normal physical examination or routine blood tests. The diagnosis of the Philadelphia chromosome abnormality by molecular studies is important test for diagnosis of CML. European Treatment and Outcome Study score is able to predict the probability of achieving a complete response after tyrosine kinase inhibitors therapy. Dynamic response assessment is essential to identify patients at high-risk of disease progression, who may benefit from a change of therapy.

Aims and Objectives

To evaluate Haematological and Molecular response after giving tyrosine kinase inhibitors therapy at 6months and 12months follow up.

Material and Methods

Present study was conducted at tertiary care hospital from June 2019 to May 2021. For this purpose, all diagnosed patients of chronic myeloid leukemia were enrolled and were kept on follow up for one year to assess prognosis by Hematological and Molecular response of the disease at 6 months and 12 months.

Exclusion Criteria

Hypersensitivity/ Intolerance to the Imatinib

It is an observational and longitudinal study. Data thus obtained were analysed statistically. The data were presented by mean ± standard deviation for continuous variables and frequencies with their respective percentages were given for categorical variables. Correlation coefficient was used to measure the degree of association between two variables. A p value <0.05 was considered as statistically significant.

Results

The present study was conducted on 80 diagnosed patients of Chronic Myeloid Leukemia.

Table 1: Showing demographic, clinical, hematologic characteristics, EUTOS†† risk stratification of the study group

Patient's Characteristics	Results (%)
Age (mean ± SD) (years)	44.34 +/- 14.05
Gender (M: F)	1:1
Symptoms	
Abdominal Discomfort	36.3
Decrease Appetite	12.5
Fever	22.5
Weakness	11.3
Weight Loss	8.8
Others	8.8
Hemoglobin levels (g/dl)	
<10.5 g/dl	67.5
>=10.5 g/dl	32.5
Mean Hemoglobin	9.79 +/- 2.02
Total Leucocytes Count (cells/mm^3)	
<4000	5.0
4000-11000	11.3
>11000	83.8
Mean Leucocytes	151948.38 +/- 129952.605
Platelets Counts (cells/µl)	
<1,50,000	12.5
1,50,000-4,50,000	62.5
>4,50,000	25.0
Mean Platelets	368562.50 +/- 223785.150
Spleen Size (cm)	
Normal (<13cm)	16.3
Mild to Moderate splenomegaly (13-18cm)	46.3
Massive splenomegaly (>18cm)	37.5
Mean Spleen Size	16.74 +/- 3.93
Hepatomegaly	
Yes (>12cm)	33.8
No (<=12cm)	66.3
EUTOS GROUP	
High (>87)	31.3
Low (<=87)	68.8

(††EUTOS: European Treatment and Outcome Study score, It is able to predict the probability of achieving a complete cytogenetic response (CCyR) after tyrosine kinase inhibitors (TKIs) therapy which is the strong and most confirmed surrogate survival marker. Patients without complete cytogenetic response (CCyR) after18 months of treatment with TKIs are less likely to achieve one later and are at a high risk of blastic transformation of disease. The strongest predictors for complete cytogenetic response (CCyR) at 18 months are spleen size and percentage of basophils. Spleen size is measured in cm under the costal margin, basophils as their percent in peripheral blood. Both need to be assessed at baseline. Their relationship to complete cytogenetic response (CCyR) is expressed by the formula: **7*basophils+4*spleen size.** If the sum is greater than 87, the patient is at high risk of not achieving a complete cytogenetic response (CCyR) at 18 months, while a sum less than or equal to 87 indicates a low risk. Percentage of basophils and Spleen size must be noted before any treatment.[1])

All patients included in the study population were treated with Imatinib 400mg OD to low-risk group and 400mg BD to high-risk group and assessment of their hematologic and molecular response were carried out over 6 months and 12 months thereafter.

Table 2: Showing various treatment responses after Tyrosine kinase inhibitors therapy at 6months and 12 months follow up.

Type of Response	Percentage (%)
Hematological Response (HR) at 6 months	
Complete Hematological Response (CHR)	83.8
No Hematological Response	16.3
Molecular Response (MR) at 6 months	
Complete Molecular Response (CMR)	36.3
Major Molecular Response (MMR)	16.3
No Molecular Response	47.5
Hematological Response (HR) at 12 months	
Complete Hematological Response (CHR)	88.8
No Hematological Response	11.3
Molecular Response (MR) at 12 months	
Complete Molecular Response (CMR)	71.3
Major Molecular Response (MMR)	16.25
No Molecular Response	12.5

Table3: Showing there is no age, gender, clinical presentation, hematological parameters and EUTOS risk stratification based difference in therapeutic hematological response at 6months and 12 months follow up after Imatinib therapy.

Table 3: Cross-tabulation results of patient characteristics and Hematological Response

Patient's Characteristics	Hematological Response (HR)**					
	At 6 months follow up			At 12 months follow up		
	No HR (%)	CHR* (%)	p-value	No HR (%)	CHR (%)	p- value
Age						
<= 30 years	13.3	86.7		0	100	
31-60 years	16.7	83.3	0.937	14.8	85.2	0.267
>60 years	18.2	81.8		9.1	90.2	
Gender						
Female	10	90		5.0	95.0	0.077
Male	22.5	77.5	0.130	17.5	82.5	
Haemoglobin (g/dl)						
<10.5	13.0	87.0	0.251	11.1	88.9	0.855
>= 10.5	23.1	76.9		11.5	88.5	
TLC (cells/mm³)**						
<4000	0	100		0	100	
4000-11000	33.3	66.7	0.248	33.3	66.7	0.072
>11000	14.9	85.1		9.0	91.0	
Platelets (/mm³)						
<150000	40	60.0		20.0	80.0	
150000-450000	14.0	86.0	0.086	12.0	88.0	0.454
>450000	10.0	90.0		5.0	95.0	
Spleen size (cm)						
Normal (<13cm)	7.7	92.3		7.7	92.3	
Mild to Moderate splenomegaly (13-18cm)	18.9	81.9	0.639	8.1	91.9	0.494
Massive splenomegaly (>18cm)	16.7	83.3		16.7	83.3	
Hepatomegaly						
Yes (>12cm)	11.1	88.9	0.374	14.8	85.2	0.471
No (<=12cm)	18.9	81.1		9.4	90.6	
EUTOS group**						
Low (<=87)	12.7	87.3	0.205	10.9	89.1	0.886
High (>87)	24.0	76.0		12.0	88.0	

(**HR: Hematological Response, *CHR: Complete Hematologic Response, ††EUTOS: European treatment and outcome study score, ‡‡TLC: Total leucocytes counts)

(*CHR: A complete hematologic response: It is achieved when laboratory values return to normal levels i.e. white blood cell count <10,000/mm^3 with normal differential cell count and platelet count <450,000/mm^3)

Table 4 Showing significant correlation were seen between EUTOS score and various Molecular responses at 6 months and 12 months follow up after therapy with p value of 0.036 and 0.020 respectively, which are significant.

Table 4: Cross-tabulation results of patient characteristics and Molecular Response

Patient's Characteristics	Molecular Response							
	At 6 months follow up				At 12 months follow up			
	No MR*	MMR‡	CMR†	p-value	No MR	MMR	CMR	p-value
Age								
<= 30 years	26.7	33.3	40.0		0	6.7	93.3	
31-60 years	53.7	9.3	37.0	0.122	16.7	18.5	64.8	0.276
>60 years	45.5	27.3	27.3		9.1	18.2	72.7	
Gender								
Female	40.0	17.5	42.5	0.389	7.5	12.5	80.0	0.207
Male	55.0	15.0	30.0		17.5	20.0	62.5	
Hb (g/dl)**								
<10.5	46.3	14.8	38.9	0.748	13.0	22.2	64.8	0.098
>= 10.5	50.0	19.2	30.8		11.5	3.8	84.6	
TLC‡‡ (cells/mm^3)								
<4000								
4000-11000	50.0	25.0	25.0		0	25.0	75.0	0.338
>11000	44.4	11.1	44.4	0.955	33.3	11.1	55.6	
	47.8	16.4	35.8		10.4	16.4	73.1	
Platelets (/mm^3)								
<150000	70.0	20.0	10.0		20.0	20.0	60.0	
150000-450000	46.0	16.0	38.0	0.434	14.0	18.0	68.0	0.577
>450000	40.0	15.0	45.0		5.0	10.0	85.0	
Spleen size (cm)								
Normal (<13cm)	46.2	23.1	30.8		7.7	0	92.3	
Mild to Moderate splenomegaly (13-18cm)	43.2	13.5	43.2	0.766	10.8	16.2	73.0	0.273
Massive splenomegaly (>18cm)	53.3	16.7	30.0		16.7	23.3	60.0	
Hepatomegaly								
Yes (>12cm)	44.4	18.5	37.0	0.898	14.8	18.5	66.7	0.809
No (<=12cm)	49.1	15.1	35.8		11.3	15.1	73.6	
EUTOS†† group	41.8	12.7	45.5	0.036	10.9	9.1	80.0	0.020
Low (<=87)	60.0	24.0	16.0		16.0	32.0	52.0	
High (>87)								

Patient's Characteristics	Molecular Response							
	At 6 months follow up				At 12 months follow up			
	No MR*	MMR‡	CMR†	p-value	No MR	MMR	CMR	p-value
Age								
<= 30 years	26.7	33.3	40.0		0	6.7	93.3	
31-60 years	53.7	9.3	37.0	0.122	16.7	18.5	64.8	0.276
>60 years	45.5	27.3	27.3		9.1	18.2	72.7	
Gender								
Female	40.0	17.5	42.5	0.389	7.5	12.5	80.0	0.207
Male	55.0	15.0	30.0		17.5	20.0	62.5	
Hb (g/dl)**								
<10.5	46.3	14.8	38.9	0.748	13.0	22.2	64.8	0.098
>= 10.5	50.0	19.2	30.8		11.5	3.8	84.6	

(MR*: Molecular response, MMR‡: Major molecular response, CMR†: Complete molecular response, Hb**: Haemoglobin levels, TLC§: Total leucocytes count, EUTOS††: European Treatment and Outcome Study score)

(Molecular response (MR) analysis requires a peripheral blood sample study.MR2 is 2 log reduction of BCR-ABL from baseline of standardized international scale and it is equivalent to complete cytogenetic response (CCyR).MR3 (MMR: Major Molecular Response) is 3 log reduction of BCR-ABL from baseline of standardized international scale and it corresponds to <0.1% BCR-ABL on the IS.[13]MR4/5 is Complete Molecular Response (CMR) where BCR-ABL levels are undetectable in peripheral blood [(2)])

Table 5 showing that at the end of study we found a significant positive correlation between the molecular response at 12 months with haemoglobin level at presentation and significant reverse correlation between molecular response at 12 months with age of patient, spleen size and EUTOS score.

Table 5: Correlations between patient characteristics and molecular response at 12 months follow up

Patient Characteristics	Molecular Response at 12 Months	
	R	p-value
Age of patient	-0.242	0.030
Hemoglobin on presentation	+0.236	0.035
Spleen size	-0.278	0.013
EUTOS†† score	-0.270	0.015

(EUTOS††: European Treatment and Outcome Study score)

Discussion

The present observational and longitudinal study was conducted with the aim of evaluating Molecular response after giving Imatinib (TKIs) therapy at 6 months and 12 months follow up.In the study population, out of 80 patients in the study population 40 were females and 40 were males with M: F is 1:1 which was in contrast to study conducted by Hoglund M et al[(3)]which showed male/female ratio of 1.2-1.7 and study by Eden RE et al[(4)] showed slight male predominance. Out of total 80 patients maximum patients (54) were in 31-60 years age group followed by patients (15 out of 80) in </= 30 years age group. Minimum patients (11 out of 80) were in age group of > 60 years. The Mean age group of study population was 44.34 years and Median age of presentation was 42 years in our study. Most literature from western studies show median age of presentation is 55 years (European) and 66 years (Americans). Thus, the age of presentation of CML in Indian population is decade earlier from Western population.[(5)] The median age of our study is comparable with study conducted by Kumar et al[(6)]in and around UP, India which showed median age of presentation is 37 years. The disease can manifest at any age. The difference could be attributed to demographic characteristics of developing countries or genetic factors. In the study population among various

symptoms, 29(36.3%) patients had abdominal discomfort, 18(22.5%) patients had fever, 10(12.5%) had decreased appetite, 9(11.3%) patients had weakness, 7(8.8%) patients had weights loss and 7 (8.8%) patients had other complaints like headache, loose stools, dyspnea, vomiting etc. Thus, our study showed most common symptom of presentation is abdominal discomfort followed by fever, which is similar to the studies conducted by Kumar S et al[6]and Syed NN et al.[7] Mean hemoglobin, TLC and platelet counts of our study population was 9.7 g/dl, 151x10 ^{9}/l and 368x10^{9} respectively. Laboratory parameters of study conducted by Syed NN et al[7] revealed mean haemoglobin was 10.0 g/dl, mean total leukocyte count was 168 x 10^{9}/l and mean platelets 408 x 10^{9}/l. Mean spleen size in study population is 16.74 cm. Out of total 80 patients, 83.8% patients had spleenomegaly (37.5% patients had massive splenomegaly and 46.3% patients had mild to moderate splenomegaly) and 16.3% patients had normal spleen size. Srinivas KG et al[8]in their study showed 70% patients had spleenomegaly and Ahmed R et al[9]in their study showed that 82.2% patients had spleenomegaly. Out of total 80 patients, 33.8% patients had hepatomegaly and 66.3% patients had normal size liver. Srinivas KG et al[8]in their study showed 20% patients had hepatomegaly and Kumar S et al[6]in their study showed 52% patients had hepatomegaly. Out of total 80 patients, 25 (31.3%) patients had high EUTOS score and 55 (68.8%) patients had low EUTOS score. On 6 months follow up 83.8% patients had Complete Hematological Response and 16.3% patients had No Hematological Response and on 12months follow up 88.8% patients had Complete Hematological Response and 11.3% patients had No Hematological Response. No significant correlation was seen between the hematologic response and the patient's age, gender, clinical presentation, laboratory values of haemoglobin, TLC, platelets count, hepatospleenomegaly and EUTOS score at the time of presentation which is in comparison to the study conducted by Razmkhah F et al[10] in which 30 diagnosed patients of Chronic myeloid leukaemia (all in chronic phase) were followed up after Imatinib therapy for hematological response which showed 90% patients achieved CHR at 8 month follow up and their study also did not find any significant correlation between response and patient's age , gender or laboratory values. A study conducted by Nasser A et al[11]showed that at 12 months follow up after Imatinib therapy 68.5% patients achieved CHR.On 6 months follow up 36.3% patients had Complete Molecular Response, 16.3% patients had Major Molecular Response and 47.5% patients had No Molecular Response but on 12 months follow up 71.3% patients had Complete Molecular Response, 16.25% patients had Major Molecular Response and 12.5% patients had No Molecular Response. A study conducted by Razmkhah F et al[8] showed 46.7% patient showed CMR and 53.3% patients showed no molecular response at 8 month follow up after Imatinib therapy. A significant correlation was seen between EUTOS score and various Molecular responses at 6 months and 12 months follow up after Imatinib therapy 400mg OD to low EUTOS score group patients and 400mg BD to high EUTOS score group patients with p value of 0.036 and 0.020 respectively. At the end of study i.e., at 12 months follow up we found a significant positive correlation between the molecular response at 12 months with haemoglobin level at presentation and significant reverse correlation between molecular response at 12 months with age of patient, spleen size and EUTOS score. At 12 months follow up 83.8% patients had

Complete hematological response but only 71.3% patients had Complete Molecular Response. Therefore, it is clear that patient and therapy monitoring based on hematologic response alone can be misleading and will compromise physicians' judgment.

Conclusion

Till now European Treatment and Outcome Study (EUTOS) score which is able to predict the probability of achieving a complete cytogenetic response (CCyR) after tyrosine kinase inhibitors (TKIs) therapy which is the strong and most confirmed surrogate survival marker. Patients without complete cytogenetic response (CCyR) after18 months of treatment with TKIs are less likely to achieve one later and are at a high risk of blastic transformation of disease. With our study results we can consider EUTOS score to predict molecular response after 12 months of treatment with TKIs. The plus point of considering molecular response over cytogenetic response is that molecular response is evaluated from peripheral blood sample quantitative analysis of BCR-ABL by RT-PCR, on the other side cytogenetic response evaluation requires bone marrow sample analysis for evaluation of >20 metaphases for the Ph+ chromosome.At 12 months follow up 83.8% patients had complete hematological response but only 71.3% patients had Complete Molecular Response. Therefore, it is clear that patient and therapy monitoring based on hematologic response alone can be misleading and will compromise physician's judgment.Determining the patient's response to therapy helps to evaluate the course of therapy and makes it possible to be a few steps ahead in case of any complication and if patient is not achieving molecular response, then we can plan for Imatinib Resistant Mutation Analysis (IRMA) and switch to other second or third line tyrosine kinase inhibitor.

Limitations

First limitation of our study is small sample size. Second limitation is that all patients included in study sample were in chronic phase of disease. None of the patient was in accelerated or blast crisis phase of the disease. Thus, this study correlates EUTOS score and molecular response of CML patients in chronic phase of the disease.

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