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EFFECT OF AGE AND SEX UNDER IMATINIB MESYLATE THERAPY ON CHRONIC MYELOID LEUKAEMIA PATIENTS: A PILOT STUDY FROM INDIA

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ABSTRACT: Among adults in India, Chronic myeloid leukemia (CML) is most common leukemia and accounts for 30% to 60% of all adult leukemias. Imatinib mesylate induces the highest rate of complete hematological and cytogenetic responses, but its efficacy is still debated in different sets of patients. Total 50 newly diagnosed patients of CML were enrolled. Patients receiving imatinib 400mg orally daily were monitored carefully for haematological changes and changes were noted at 3, 6 and 9 month. Patients were categorized on the basis of age and gender, and hematological and cytogenetic responses were compared. Cytogenetic studies were done at 6 months to ascertain the response. Imatinib produced >80% response in various hematological parameters in different groups of patients. Younger age group and male patients shows better hematological as well as cytogenetic response at 6 months. Older age group and female patients shows poor responses in comparison to younger age group and male patients of CML. Further study on large samples of CML patients is advised to search out the possible reasons of such differences.

INTRODUCTION: Chronic myelogenous leukaemia also known as Chronic myeloid leukaemia (CML), characterized by formation of too many haematopoietic cells is a myeloproliferative disorder which carries the Philadelphia chromosome. The association between BCR-ABL molecular expression and the Philadelphia chromosome and its pathophysiology has introduced the research strategies to suppress the Ph cells or BCR-ABL expression.

The Molecular studies has proved the role of active protein tyrosine kinase^{1,2}. This finding led to the emergence of imatinib mesylate, a tyrosine kinase inhibitor (TKI). Imatinib Mesylate having its mechanism of action in which it particularly binds to the ATP binding site of the BCR-ABL kinases and inhibits the tyrosine kinase signalling pathway. Various clinical studies on imatinib reported with an effective result in form of complete hematological remission nearly in all patients and cytogenetic responses in several patients^{3,4}.

Chronic myeloid leukemia (CML) is the most common leukemia in India⁵. The prevalence of CML cases are reported mostly in adults and uncommon in younger adults but very rarely affects the children.

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Older age people have shown consistent poor prognosis with Philadelphia chromosome positive chronic myeloid leukaemia⁶⁻⁸ and has been a consistently poor prognostic factor for outcome in patients with Ph-positive CML. Several prognostic models previously reported that older age was an independent poor prognostic factor for outcome in patients with CML^{9,10}.

The present study focused on the prognosis of older age patients as well as the outcomes in different gender in the era of imatinib therapy. As per our knowledge, no research study has been performed regarding the effect of sex on the clinical response in CML patients with Philadelphia chromosome positive under imatinib mesylate therapy.

MATERIALS AND METHODS:

Study design: In this prospective observational cross sectional single centered study, a total of 50 patients of CML were enrolled at S.S. Hospital and Research Institute, Kankarbagh (Patna), Bihar, India. The data were collected during the period of August 2015 to May 2016. The study protocol was approved by the ethical committee of the institute and signed informed consent were obtained from all the patients included in the study.

Selection criteria:

The inclusion criteria were as follows:

- Age of patients were above 18 years.
- All patients were Philadelphia (Ph) chromosome positive CML.
- Patients who agreed to give their consent.

The exclusion criteria were as follows:

- Ph chromosome negative CML patients.
- Pregnant women or nursing mothers.
- Patients with co-morbid condition like diabetes mellitus, hypertension and severe cardiovascular diseases.
- Patients suffering with HIV and other infectious chronic disorders.

Hematological parameters used for selection:

Percentage of blast cells or basophils in the peripheral blood or bone marrow $\leq 15\%$, percentage of blast plus promyelocytes in the peripheral blood or bone marrow $< 30\%$, and platelet count $\geq 100 \times 10^9/L$.

Evaluation of parameters: As per the standard protocol, the doctor had prescribed oral imatinib of 400 mg/day to all CML patients of chronic phase. Complete haematological tests were done once in 2 weeks during the first month and there after monthly. Cytogenetic test was done at every 3, 6 and 9 month. In this study, the cytogenetic data was assessed at 6th month. Cytogenetic analysis was done by using interphase FISH technique.

Response criteria: Complete hematological response (CHR) was defined as a total leukocyte count $< 10 \times 10^9/L$, platelet count $< 450 \times 10^9/L$, myelocytes and metamyelocytes $< 5\%$, no blast or promyelocytes, in addition to disappearance of all sign and symptoms of CML.

Cytogenetic response (CR) was classified into four types depending upon the percentage of residual Ph chromosome positive metaphase in conventional cytogenetics: no cytogenetic response ($> 90\%$ Ph chromosome-positive cells), minor CR (35-90%), major CR (1-34%) and complete CR (0%).

Statistical analyses: The data were analyzed using statistical Package for Social Sciences (SPSS), and were expressed as mean \pm standard deviation. The comparison of the mean values was done by using paired and unpaired t-test, and the differences were considered statistically significant if $P < 0.05$.

In **Table 1** the baseline characteristics of the study participants are mentioned according to their age (i.e. < 65 years and ≥ 65 years). The mean age of < 65 years and ≥ 65 years of study participants was observed 44 year and 65 year, respectively.

TABLE 1: CHARACTERISTICS OF CML PATIENTS OF CHRONIC PHASE

Characteristics	< 65 years	≥ 65 years
Patient numbers- n (%)	26 (52%)	24 (48%)
Sex- n (%)		
Male	18 (69.2%)	14 (58.3%)
Female	8 (30.8%)	10 (41.7%)
Age range (in years)	22 - 56	60 - 75
Mean age (in years) at the time of starting imatinib (mean \pm SD)	44 \pm 10.9	65 \pm 4.87

Hematological response: The patients of CML were stratified into two groups: 26 patients (52%) were less than 60 year as younger age, while 24 patients (48%) were of older age, i.e. more than 65 years. The hematological parameters of younger

and older age patients were compared and shown in **Table 2**. The percent reduction of TLC, granulocyte, myelocyte, metamyelocyte, and promyelocyte in younger age patients of CML were comparatively better than the older age CML patients throughout the successive follow up at 3, 6 and 9 month, but in case of blast cells, the percentage reduction was observed more in CML patients of older age at 3 month. From 6 month onwards and finally at 9 month, the result was quite similar in both age group of CML patients in form

of complete reduction of blast cells. In case of platelet and haemoglobin, percentage platelet improvement was relatively better in older age CML patients at 3 and 6 month, but at 9 month the percentage improvement was almost same as of younger age. The percentage improvement for haemoglobin was observed better in younger age throughout the successive follow up periods. On 9 month, there was decrease of percentage haemoglobin observed in older age CML patient.

TABLE 2: COMPARATIVE ANALYSIS OF HEMATOLOGICAL PARAMETER IN TWO DIFFERENT AGE GROUP PATIENTS OF CHRONIC MYELOID LEUKAEMIA WITH PRE-TREATMENT AND FOLLOW UP (PERCENT CHANGE) UNDER IMATINIB (400 MG) THERAPY

Parameters	Age in years	Pre treatment Mean \pm SD	Percent change (after 3 Months) Mean \pm SD	Percent change (after 6 Months) Mean \pm SD	Percent change (after 9 Months) Mean \pm SD
Total Leukocyte Count ($10^9/L$)	<65 yrs.	113.93 \pm 66.00	- 89.87 \pm 4.03	- 92.93 \pm 2.96	- 95.31 \pm 5.49
	\geq 65 yrs.	86.20 \pm 32.38	- 76.86 \pm 50.55	- 85.26 \pm 29.91	- 88.41 \pm 24.80
Platelet ($10^9/L$)	<65 yrs.	310.23 \pm 129.67	39.86 \pm 137.80	49.61 \pm 180.92	71.13 \pm 30.06
	\geq 65 yrs.	357.17 \pm 169.60	55.69 \pm 17.69	62.13 \pm 20.45	71.74 \pm 24.54
Haemoglobin (g/dl)	<65 yrs.	9.86 \pm 1.83	19.39 \pm 19.85	26.22 \pm 27.88	29.93 \pm 30.06
	\geq 65 yrs.	9.023 \pm 1.24	17.69 \pm 21.90	25.59 \pm 26.62	16.83 \pm 16.40
Granulocyte in %	<65 yrs.	76.40 \pm 6.13	- 13.47 \pm 8.55	- 28.70 \pm 13.53	- 17.70 \pm 7.67
	\geq 65 yrs.	69.04 \pm 9.41	- 7.94 \pm 15.15	- 16.35 \pm 18.08	- 15.10 \pm 10.64
Blast Cells	<65 yrs.	8.19 \pm 3.08	- 63.90 \pm 20.96	- 100.00 \pm 0.00	- 100.00 \pm 0.00
	\geq 65 yrs.	8.37 \pm 3.85	- 74.29 \pm 18.80	- 100.00 \pm 0.00	- 100.00 \pm 0.00
Myelocytes	<65 yrs.	15.31 \pm 3.64	- 65.06 \pm 16.18	- 94.97 \pm 6.50	- 96.34 \pm 5.08
	\geq 65 yrs.	16.63 \pm 7.50	- 53.45 \pm 27.41	- 94.59 \pm 7.66	- 94.31 \pm 10.35
Metamyelocytes	<65 yrs.	8.19 \pm 2.82	- 55.61 \pm 12.22	- 96.06 \pm 6.46	- 96.53 \pm 7.75
	\geq 65 yrs.	9.50 \pm 2.60	- 62.84 \pm 19.75	- 91.04 \pm 13.24	- 96.50 \pm 6.43
Promyelocytes	<65 yrs.	14.35 \pm 2.97	- 60.85 \pm 17.64	- 92.56 \pm 9.43	- 99.31 \pm 2.42
	\geq 65 yrs.	14.88 \pm 0.25	- 52.98 \pm 25.25	- 87.15 \pm 14.41	- 96.77 \pm 6.50

(-) sign shows % reduction of cell numbers from its pre-treatment value

In **Table 3**, we stratified the whole patients of CML according to gender, in which there were 32 males and 18 females. We analysed the various hematological parameters of male and female patients of CML. The data shows that percentage reduction of TLC in male patients was observed comparatively better than female patients at successive follow up at 3, 6 and 9 months. Observations regarding granulocyte it was higher in female patients than male patients at 3 month and further better observed at 9 month. Percentage reduction of blast cells in female patients was observed better than male patients at 3 month and

further after follow up at 6 and 9 month, result was quite similar with 100% reduction of blast cells. In case of myelocyte, metamyelocyte and promyelocyte the percentage reduction rate was almost similar in both male and female patients of CML. For platelet and haemoglobin, percentage improvement of platelet was comparatively higher in male than female patients of CML throughout the successive follow up at 3, 6 and 9 month. For haemoglobin, percentage improvement was comparatively better in female patients at 6 and 9 month.

TABLE 3: COMPARATIVE ANALYSIS OF HAEMATOLOGICAL PARAMETER IN MALE AND FEMALE PATIENTS OF CHRONIC MYELOID LEUKAEMIA WITH PRE-TREATMENT AND FOLLOW UP (PERCENT CHANGE) UNDER IMATINIB (400 MG) THERAPY

Parameters	Sex	Pre treatment Mean \pm SD	Percent change (after 3 Months) Mean \pm SD	Percent change (after 6 Months) Mean \pm SD	Percent change (after 9 Months) Mean \pm SD
Total Leukocyte Count ($10^9/L$)	Male	94.65 \pm 30.79	- 88.26 \pm 4.99	- 91.90 \pm 3.10	- 92.65 \pm 3.20
	Female	111.22 \pm 80.46	- 75.40 \pm 58.72	- 84.56 \pm 34.20	- 86.51 \pm 28.55
Platelet ($10^9/L$)	Male	351.56 \pm 178.66	28.24 \pm 128.35	35.65 \pm 145.25	51.74 \pm 24.54
	Female	299.33 \pm 151.03	19.09 \pm 54.56	31.53 \pm 77.02	35.79 \pm 70.04
Haemoglobin (g/dl)	Male	9.65 \pm 1.70	20.23 \pm 20.96	23.31 \pm 24.62	19.60 \pm 22.33
	Female	9.11 \pm 1.42	15.63 \pm 20.37	36.99 \pm 26.31	23.00 \pm 28.39
Granulocyte %	Male	73.91 \pm 8.26	- 10.75 \pm 11.08	- 25.14 \pm 16.19	- 15.10 \pm 10.64
	Female	72.15 \pm 8.9	- 70.53 \pm 25.42	- 18.52 \pm 17.76	- 23.80 \pm 10.78
Blast Cells	Male	7.06 \pm 3.37	- 67.96 \pm 17.55	- 100.00 \pm 0.00	- 100.00 \pm 0.00
	Female	8.83 \pm 3.51	- 56.53 \pm 16.48	- 100.00 \pm 0.00	- 100.00 \pm 0.00
Myelocytes	Male	14.19 \pm 4.57	- 59.29 \pm 22.74	- 94.76 \pm 7.49	- 94.31 \pm 10.35
	Female	14.06 \pm 2.94	- 59.85 \pm 23.61	- 94.84 \pm 6.26	- 98.20 \pm 3.58
Metamyelocytes	Male	8.00 \pm 2.87	- 66.41 \pm 7.23	- 93.60 \pm 9.46	- 96.50 \pm 6.43
	Female	7.61 \pm 2.47	- 63.55 \pm 22.83	- 93.74 \pm 12.40	- 95.46 \pm 6.93
Promyelocytes	Male	14.94 \pm 2.67	- 54.32 \pm 24.12	- 89.06 \pm 13.68	- 97.52 \pm 5.84
	Female	14.44 \pm 3.12	- 61.96 \pm 16.29	- 91.56 \pm 9.35	- 99.10 \pm 2.59

(-) sign shows % reduction of cell numbers from its pre-treatment value

Cytogenetic response: In Table 4, the patients of CML were divided in two different age group, as categorised for haematological response. The Philadelphia positive cells observed at baseline and after 6 month of imatinib mesylate therapy. We observed that percentage reduction of Philadelphia positive cell was higher in younger age patients of CML than the older age patients.

TABLE 4: COMPARATIVE ANALYSIS OF CYTOGENETIC PARAMETER IN TWO DIFFERENT AGE GROUP OF CHRONIC MYELOID LEUKAEMIA PATIENTS WITH PRE-TREATMENT AND FOLLOW UP (PERCENT CHANGE) UNDER IMATINIB (400 MG) THERAPY

Parameters	Age in years	Pre treatment Mean \pm SD	Follow up in % form at 6 th Month Mean \pm SD
Philadelphia positive cells	< 65 (n = 26)	106.60 \pm 24.86	- 59.27 \pm 10.67
	\geq 65 (n = 24)	108.54 \pm 25.51	- 52.47 \pm 11.8

In Table 5, we did the comparative cytogenetic analysis in male and female patients of CML. We observed that percentage reduction of Philadelphia positive cell was high in female patients.

TABLE 5: COMPARATIVE ANALYSIS OF CYTOGENETIC PARAMETER IN MALE AND FEMALE PATIENTS OF CHRONIC MYELOID LEUKAEMIA WITH PRE-TREATMENT AND FOLLOW UP (PERCENT CHANGE) UNDER IMATINIB (400 MG) THERAPY

Parameters	Sex	Pre treatment Mean \pm SD	Follow up in % form at 6 th month Mean \pm SD
Philadelphia positive cells	Male (n = 32)	106.25 \pm 26.33	- 55.86 \pm 12.18
	Female (n = 18)	110.00 \pm 22.65	- 56.64 \pm 11.07

In Table 6 and Table 7, we classified the cytogenetic response into four types as complete cytogenetic response (CCR), major cytogenetic response (MCR), minor cytogenetic response (MiCR) and poor cytogenetic response (PCR). The data were compared at 6 month. The complete cytogenetic response (CCR) and major cytogenetic response (MCR) were better in younger age patients with (15.38%) and (80.76%) than older age patient of CML with (12.5%) and (70.83%), respectively. Minor cytogenetic response was higher in older age patients of with (16.7%) than younger age patients with (3.84%). The complete cytogenetic response (CCR) and major cytogenetic response (MCR) were higher in male patients of CML with (18.75%) and (90.62%) than female patients with (16.7%) and (72.22 %). Minor cytogenetic response was observed more in female

patients of CML with (11.1%) than male patients with (9.37%).

TABLE 6: COMPARATIVE ANALYSIS OF CYTOGENETIC RESPONSE IN TWO DIFFERENT AGE GROUP PATIENTS UNDER IMATINIB MESYLATE THERAPY AT SIX MONTH

Months	Age in years	CCR	MCR	MiCR	PCR
6 th	< 65	4 (15.38%)	21 (80.76%)	1 (3.84%)	0 (0%)
6 th	≥ 65	3 (12.5%)	17 (70.83%)	4 (16.7%)	0 (0%)

CCR-Complete cytogenetic response, MCR-Major cytogenetic response, MiCR-Minor cytogenetic response, PCR-Poor cytogenetic response

TABLE 7: COMPARATIVE ANALYSIS CYTOGENETIC RESPONSE IN MALE AND FEMALE PATIENTS UNDER IMATINIB MESYLATE THERAPY AT SIX MONTH

Months	Sex	CCR	MCR	MiCR	PCR
6 th	Male	6 (18.75%)	23 (90.62%)	3 (9.37%)	0 (0%)
6 th	Female	3 (16.7%)	13 (72.22%)	2 (11.1%)	0 (0%)

CCR-Complete cytogenetic response, MCR-Major cytogenetic response, MiCR-Minor cytogenetic response, PCR-Poor cytogenetic response

DISCUSSION: The well known link between the BCR-ABL molecular events and Philadelphia chromosome (Ph) and the pathophysiology of chronic myelogenous leukemia (CML) has focused research on strategies that suppress the expression of BCR-ABL or Ph cells^{11, 12}. To achieve maximum response or minimal residual disease has been independently associated with prolongation of survival and has become the therapeutic research goal for CML. Imatinib mesylate, a selective BCR-ABL tyrosine kinase inhibitor, has proved activity in all phases of CML¹³⁻¹⁷.

In the present study, our goal was to assess the effect of age and sex on the clinical response of CML patients under Imatinib mesylate therapy. Nine month continuous treatment of CML patients with imatinib as initial therapy have evaluated in terms of hematological as well as cytogenetic response in CML patients. Imatinib resulted in a rapid normalization of peripheral blood counts in all patients and has brought about a paradigm shift in the management of CML patients³.

According to WHO, patients ≥65 years are considered as old. In the present study, patients were stratified into two subgroups: 24 patients (48%) were 65 years of age or older and 26 (52%) were less than 65 years at enrollment into the study, with the age range 60-75 and 22-56 years, respectively. In general, the median age of onset is 38-40 years in India¹⁸. Compared to 50 years in the West. In the present study the median age of the patients were 44 and 65 years in both age groups, respectively.

Among them males were slightly frequent than females as also reported in other studies¹⁹. After starting imatinib therapy, nearly all the patients in each group achieved a significant haematological and cytogenetic response at 6 months.

This data indicated the successive same response of imatinib as reported in other clinical studies. Comparative analysis of hematological parameters between two groups of patients reveal that the pre treatment values against normal values are very significant. The post treatment values of the hematological parameters are very close to the normal values and hence it can be proved that the imatinib therapy is effective specially for the CML patients.

More specifically about hematological response, we achieved >90% recovery at the end of six months in most of the concern hematological parameters which is likely to be same, reported by Jacob et al., 2007²⁰ but less than the data reported by Deshmukh et.al, 2005²¹. As reported in various clinical studies that, older age constitutes a poor prognostic factor for outcome in patients with Ph-positive CML^{2, 22, 10}. The most widely accepted staging systems for CML, the Euro score and the Sokal score^{23, 9} include age within the variables that can negatively influence the survival of CML patients. Higher incidence of poor performance status was associated with older age. The response and survival of elderly CML patients managed with effective treatment modalities still has not been fully explored.

Our analysis is focused on investigating the influence of age on various responses (hematologic and cytogenetic) in a subset of aging patients with CML under imatinib mesylate therapy. Older patients had a lower probability of CHR compared to younger ones. Cortes *et al.*²⁴ reported a higher probability of CHR (94%) in both groups of patients using the same criteria. The CHR rate observed in older patients in our study, significantly different and lower than that reported by Cortes *et al.* (94%), might be due to age group of the CML patients chosen for defining patients as elderly (60 years by Cortes *et al.*, in comparison to 65 years in the present study).

Another comparison was done to identify the difference in the Ph cells, between patients of defined two age groups. At baseline, no significant differences observed between older and younger age groups as well as in between males and females in the mean Ph cell. Significant differences were observed after six months of follow up under imatinib mesylate treatment in the Ph positive cell reduction, observed more in younger age group of patients in comparison to older age groups. Whereas, the mean levels of Ph positive cells were not significantly different in between older and younger age group of patients after six month of imatinib mesylate treatment.

The role of Ph chromosome in the development and pathogenesis of CML is well documented. Early in the chronic phase of CML, the Ph chromosome is likely the sole genetic event in the majority of patients^{25,26}. O'Dwyer *et al.*²⁷ reported recently on 15 patients in chronic-phase CML with clonal evolution noting CCRs in 9 of 15 patients (60%). However, relatively small number of patients and other factors may be responsible for it.

The comparison of responses to treatment by age group after six months: older patients had a lower probability of complete cytogenetic response (CCR) compared to younger patients. In the older age group 3/24 patients (12.5%) achieved a CCR compared with 4/26 (15.38%) patients in the younger age group. Whereas, in the older age group 17/24 patients (70.83%) achieved a MCR compared with 21/26 (80.76%) patients in the younger age group.

Further MiCR was observed more i.e. 4/24 (16.4%) in older age group of patients, in comparison to younger age groups.

Whereas, the responses to treatment after six months by deviding the patients according to their sex. The male patients had a lower probability of complete cytogenetic response (CCR) compared to female patients. In the male group 6/32 patients (18.75%) achieved a CCR compared with 3/18 (16.7%) patients in the female group. Whereas, in the male group 23/32 patients (90.62%) achieved a MCR compared with 13/18 (72.22%) patients in the female group. Further MiCR was observed more i.e. 2/18 (11.1%) in female group of patients, in comparison to males.

The above findings are nearly compatible with a study by Jacob *et al.*, 2007. Though, complete and major cytogenetic responses (CCR and MCR) are observed to be higher in the north Indian study group 53/72%²⁸ as well as in the western study groups- 69/85%²⁹ and 72/90%², in comparison to our present data. Rajappa *et al.* 2008 from Hyderabad, India showed 56% complete cytogenetic response among 201 CML patients at 29.5 months of follow-up³⁰. Lower plasma levels of imatinib may be associated with lower cytogenetic response³¹.

CONCLUSION: In conclusion, the present study demonstrates the poor prognostic influence of older age and female gender in patients suffering with CML and receiving imatinib mesylate treatment. The possible reasons could be a lower plasma levels which was reflected in the form of poor or less satisfactory hematological as well as cytogenetic responses in the above defined group of patients of CML. Further investigation is needed on large sample size to search out the causes and steps need to be taken for better care.

CONFLICT OF INTEREST: All authors report no conflict of interest in this work.

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