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Original Research Article

To Study the Clinical and Haematological Profile of CML Patients and To Compare the Haematological Response of Imatinib and Hydroxyurea in Different Subsets of CML Patients

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Abstract

Background: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that originates in an abnormal pluripotent bone marrow stem cell and is constantly associated with BCR-ABL fusion gene. The present study was undertaken to obtain the clinical and hematological profile in adult CML patient. An attempt had been made to evaluate as well as compare the response of patients to the drugs - Hydroxyurea and Imatinib Mesylate. The earlier is an S phase acting agent and acts by inhibiting DNA synthesis while the latter is a potent and selective tyrosine kinase inhibitor. ***Methods:*** This was a prospective study done between January 2000 to march 2011 in department of pathology and medicine at Banaras Hindu University. A total 50 patients were studied. Exclusion criteria- pregnant ladies and children below 16 years were not included in the study. Patients on hydroxyurea were given 1000mg/day in chronic phases while those in accelerated phase and blast crisis received 30000 mg daily. The patients in imatinib mesylate group in chronic phase received single dose of 400-mg daily, while those in accelerated phase and blast crisis received 600 to 800 mg daily. Complete blood counts were monitored weekly for the first month, fortnightly thereafter till patient achieved hematological remission and then monthly. Interchange of patients among the groups was allowed. The diagnosis was based on general blood picture and bone marrow aspiration was ever needed. The standard criteria for the diagnoses of chronic phase, accelerated phase and blast crisis were used. ***Results:*** Chronic myeloid leukemia was commoner in males (male to female ratio was 1.4. Both the drugs were not age and gender sensitive. There was no significant difference in Imatinib and hydroxyurea group in mean post treatment TLC, mean post-treatment PLT, mean post-treatment HB, and mean post treatment spleen levels of patient according to the criteria of phases of disease though side effects were significantly lower with imatinib. Imatinib mesylate, a selective inhibitor of the protein tyrosine kinase has shown promising results in chronic myeloid leukaemia in all phases. Its efficacy, specificity and the safety profile makes it a better choice for the first line therapy in CML.

Keywords: Wilms' tumor, renal, children.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that originates in an abnormal pluripotent bone marrow stem cell and is constantly associated with BCR-ABL fusion gene located in the Ph chromosome [1].

CML is most common leukemia among adults in India and accounts for 30% to 60% of all adult leukemia [2].

The only consistently successful curative treatment of CML beyond 10 yrs follow–up has been allogenic bone marrow transplantation [3]. However, stem cell transplantation has its own share of both acute and chronic toxicities and is possible only in a limited number of patients. Among the non-transplant treatment modalities, only interferon produces a cytogenetic response in 15-20% of patients but not without troublesome side effects. Imatinib mesylate shows promising results in chronic myeloid leukemia in all phases. Its efficacy, specificity and the safety profile makes it a strong contender for the first line therapy in CML [4].

Hydroxyurea is an S phase acting agent and acts by inhibiting DNA synthesis [5]. This drug, acting as an inhibitor of ribonucleotide reductase, can lower

blood counts within 1 to 2 days, especially if higher-than-standard doses are used. The advantages of hydroxyurea are the rapid onset, the lack of serious side effects and the rapid recovery of counts if excessive lowering of the WBC occurs [6-8]. The side effects of hydroxyurea are mild nausea and skin rash [1]. The usual dosage of hydroxyurea is between 500 and 3,000 mg/day; larger dosages may be required initially.

Imatinib mesylate (IM) is a potent and selective tyrosine kinase inhibitor that has become standard therapy for patients with CML [3, 9, 10].

The present study was undertaken to obtain the clinical and hematological profile in adult CML patient. An attempt had been made to evaluate as well as compare the response of patients to the drugs - Hydroxyurea and Imatinib Mesylate. There were few publications on responses of patients in CML from the Indian subcontinent.

MATERIALS AND METHODS

This was a retro prospective study done between January 2000 to march 2011 in department of pathology and medicine at Banaras Hindu University. A total 50 patients were studied. Pregnant ladies and children below 16 years were excluded from the study.

Patient's details regarding age, sex and a complete clinical history including relevant clinical manifestations like fever, weakness, abdominal pain, decreased appetite, weight loss, breathlessness, vomiting, diarrhea, cough, splenic infarct/abscess, tingling/ numbness, chest pain, weakness, bone pain, hepatomegaly, splenomegaly, lymphadenopathy and anaemia were noted. The history of therapy (duration & dose) was noted. Any change in therapy, dose and any side –effect of the drug was also noted.

Investigations like complete blood count including hemoglobin level, platelet count, total leukocyte count and differential leukocyte count were recorded at the time of diagnosis.

Patients on hydroxyurea were given 1000mg/day in chronic phases while those in accelerated phase and blast crisis received 30000 mg daily. The patients in imatinib mesylate group in chronic phase received single dose of 400-mg daily, while those in accelerated phase and blast crisis received 600 to 800 mg daily. Complete blood counts were monitored weekly for the first month, fortnightly thereafter till patient achieved hematological remission and then monthly. Interchange of patients among the groups was allowed. Usually, patients in Imatinib group were transferred to hydroxyurea group on economical ground, while patients in hydroxyurea group were transferred to Imatinib group whenever there was no response to treatment or whenever immediate relief from symptoms was needed.

The diagnosis was based on general blood picture and bone marrow aspiration was ever needed. Differential leucocytes count was done in 200 cells in peripheral blood. Blast percentage, basophil percentage and morphology of the cells were noted. Any features of dysplasia, if present were noted. The standard criteria for the diagnoses of chronic phase, accelerated phase and blast crisis were used.

Chronic Phase

Chronic phase was defined - peripheral blood shows leucocytosis (12-1000x10^9/L, median ~100x10^9/L) due to neutrophils in different stages of maturation with peaks in the percent of myelocytes and segmented neutrophils. Blast cells <10% (usually 2% of WBC in peripheral blood and <5% of nucleated cells of bone marrow). Basophils were invariably present, eosinophilia was common and absolute monocytosis may be present but < 3%. Platelet count ranges from normal to >1000x10^9/L and thrombocytopenia is uncommon.

Diagnosis of Accelerated and Blast Phase in CML [1, 3]

Accelerated phase (Diagnosis is made when ANY of the listed features is present.)

- Persistent or increasing WBC (> 10x10^9/L) and /or persistent or increasing splenomegaly unresponsive to therapy.
- Persistent thrombocytosis (> 100x10^9/L) uncontrolled by therapy.
- Persistent thrombocytopenia (< 100x10^9/L) unrelated to therapy.
- Clonal cytogenetic evolution occurring after the initial diagnostic karyotype.
- Basophils ≥ 20% in the peripheral blood.
- 10-19% myeloblasts in the blood or bone marrow.

Blast crisis

1. Blasts ≥ 20% of peripheral blood WBC or of the nucleated cells of the bone marrow or

2. Extra medullary blast proliferation.

Anaemia was diagnosed when the haemoglobin level was <12 g/dL in women and <13 g/dL in men. Thrombocytosis was diagnosed when the platelet count was >450 × 10^9/L, and thrombocytopenia was diagnosed when the platelet count was < 150 × 10^9/L.

For all statistical calculations and results, SPSS software was used. Mean, standard deviation was calculated and all significant p values were evaluated using paired t test.

Response Evaluation

Complete hematologic response (CHR) - Absence of splenomegaly, disappearance of all signs and symptoms of CML and normalization of the peripheral blood picture.

RESULTS

Median time of follow up was 36.9 ±26.37 month. In imatinib mesylate and Hydroxyurea group median time of follow up was 35.8 ± 21.77 month and 38 ± 30.71 month respectively.

15 Patient in CML-CP phase were on hydroxyurea and imatinib therapy each. 5 Patient in CML-AP phase were on hydroxyurea and imatinib treatment each while 5 Patient in CML-BC phase were on hydroxyurea and imatinib therapy each.

Chronic myeloid leukemia was commoner in males. The ratio was 1.4 (M: F). Among the patients in chronic phase, 9 (60%) males, 6 (40%) females were on Hydroxyurea therapy and 9 (60%) males, 6 (40%) females were on Imatinib therapy.

Among the patients in accelerated phase, 2 (40%) males and 3 (60%) females were on Hydroxyurea therapy while 3 (60%) male and 2 (40%) female were on Imatinib therapy.

Among the patients in blast crisis, 3 (60%) males and 2 (40%) females were on Hydroxyurea therapy and 4 (80%) males and 1 (20%) females were on Imatinib therapy.

The median age of presentation of CML was 41.26yrs. All patients were symptomatic at the time of diagnosis. The common symptoms of the patients were fullness of the abdomen (62%) fever (56%), abdominal pain (30%), and weakness (34%). Other complaints were decreased appetite (32%), weight loss (18%), body pain (12%), cough (12%), breathlessness (8%), vomiting (8%), leg pain (8%) diarrhea (6%), splenic infarct/abscess (4%) priapism (4%), tingling/numbness (4%), chest pain (2%), joint pain (2%) and pain or difficulty in micturition (2%). 2 patients had priapism. At the time of presentation, signs were splenomegaly (100%), anaemia (100%), hepatomegaly (38%) and lymphadenopathy (2%) (Table-1).

The effect of Imatinib on platelet (p=0.001), haemoglobin (p=0.0001), spleen (p=0.0001) and on WBC (p=0.0001) was significant while effect of Hydroxyurea on platelet (p=0.0001), haemoglobin (p=0.0001), spleen (p=0.0001) and on WBC (p=0.0001) was also significant.

Effect of Imatinib and Hydroxyurea on blast (p=0.0000) and basophils (p=0.0000) were also significant.

Both the drugs were not age and gender sensitive. There was no significant difference in Imatinib and hydroxyurea group in mean post treatment TLC, mean post-treatment PLT, mean post-treatment HB, and mean post treatment Spleen levels of patient according to the criteria of phases of disease. Similar result was obtained when we classified the patient according to Sokal Scoring method.

On evaluating the response of the drugs, it was seen that both the drugs were efficient in bringing hematological response. In chronic phase, 11 (73.33%) patient in imatinib group and 8 (53.33%) patient in hydroxyurea group had complete hematological response (CHR). In accelerated phase, 3 (60%) patient in imatinib group and 2 (40%) patient in hydroxyurea group had CHR. In blast crisis, 3 (60%) patient in imatinib group and 1 (20%) patient in hydroxyurea group had CHR (Table-2).

In chronic phase, 4 (26.67%) patient in imatinib group and 7 (46.67%) patient in hydroxyurea group had partial hematologic response (PHR). In accelerated phase, 2 (40%) patient in imatinib group and 3 (60%) patient in hydroxyurea group had PHR. In blast crisis, 2 (40%) patient in imatinib group and 4 (80%) patient in hydroxyurea group had PHR.

17 patients each of imatinib group and hydroxyurea group were on continuous therapy, while 8 patients each of imatinib group and hydroxyurea group were on discontinuous therapy or had to be transferred to the other group for at least some-time during the study period. 10 patients in imatinib group and 11 patients in hydroxyurea group were on continuous therapy in CML chronic phase. While 4 patients of imatinib group and 3 patients of hydroxyurea group were on continuous therapy in CML-AP. 3 patients of imatinib group and 3 patients of hydroxyurea group were on continuous therapy in CML-BC. In CML-CP, 5 patients of imatinib group and 4 patients of hydroxyurea group were on dis-continuous therapy or transferred to the other group. In CML-AP, 1 patients of imatinib group and 2 patients of hydroxyurea group were on dis-continuous therapy or transferred to the other group. In CML-BC, 2 patients of imatinib group and 2 patients of hydroxyurea group were on dis-continuous therapy or transferred to the other group.

In hydroxyurea group, 15 out of 25 cases had blacking of nails and body. In imatinib group, 8 out of 25 patients had increase in weight gain which was also the most common side-effect. 2 had oral ulcer and 2 had skin rashes. Out of 50 cases, symptoms persisted in only 9 patients. Most common persistent symptom was fullness of the abdomen seen in 3 patients each in hydroxyurea and imatinib group respectively. Further in hydroxyurea group, weight loss, body pain and pain abdomen was found in 1 patient each (Table-3).

Development of new symptoms and signs were seen in 9 patients. One patient was of imatinib group while 8 patients were of hydroxyurea group. Most common developed new clinical manifestation in hydroxyurea group was joint pain/ leg pain seen in 6 (24%) cases. Increase in platelet counts was seen in 4

(16%) patients. 2 (8%) patients had body pain, 1 (4%) had increase in TLC counts and 2 (8%) had anaemia. In imatinib group, 1 (4%) patient had pancytopenia (Table-3).

Table-1: Clinical and hematological findings among CML patients- at the time of diagnosis

WBC(1000/ml)	N	%
<20	5	10
29-99	15	30
100-249	16	32
250-350	15	30
>350	2	4
HB(gm/dl)	N	%
≤7.5	8	16
7.6-9.4	17	34
9.5-11.4	14	28
≥11.5	11	22
PLT(1000/ml)	N	%
<50	0	0
50-149	11	22
150-449	27	54
450-599	6	12
600-999	6	12
>1000	0	0
Spleen (in cm)	N	%
1-4	1	2
5-8	24	48
9-12	20	40
≥13	5	10
Blasts(in numbers)		
0	3	6
1-9	27	54
10-19	10	20
20-29	2	4
30-39	3	6
40-49	2	4
50-59	2	4
≥60	1	2
Basophils(in numbers)		
0-1	6	12
2-5	23	46
≥6	21	42

Table-2: Haematological response seen by both the drugs

	Hydroxyurea			**Imatinib**		
	CP	**AP**	**BC**	**CP**	**AP**	**BC**
CHR	8(53.33%)	2(40%)	1(20%)	11(73.33%)	3(60%)	3(60%)
PHR	7(46.67%)	3(60%)	4(80%)	4(26.67%)	2(40%)	2(40%)

DISCUSSION

The mean age of patients in CML-CP in various Indian studies ranged from 36.2 to 40.47 years while in an international study it was 47.1 years. In our study, mean age in CML-CP patients was 41.26±13.97, which was in agreement with Indian studies but lower when compared to international studies. Thus, mean age of presentation in India is lower than other countries.

The male to female ratio of patients in CML-CP in our study was 1.5:1. Male preponderance was seen in all the Indian as well as all international studies (Table-4).

Fever was present in 56% cases in our study which was comparable to all Indian studies. Fever was only seen in 6.2% cases in Savage ET al study [11]. This can probably be explained by the fact that infection rate is very low in western countries as compared to India.

Table-3: Adverse effects of the drugs on patients

Adverse Effects	Hydroxyurea				Imatinib			
	CP	AP	BC	Total n (%)	CP	AP	BC	Total n (%)
Nail blackning	7	5	3	15 (60)	0	0	0	0
Weight gain	0	0	0	0	4	2	2	8(32)
Oral ulcer	0	0	0	0	1	1	0	2(8)
Skin rashes/nodules	0	0	0	0	0	2	0	2(8)
Joint /leg pain	2	0	4	6(24)	0	0	0	0
Body Pain	2	0	0	2(8)	0	0	0	0
TLC-IN	0	1	0	1(4)	0	0	0	0
PLT – IN	0	3	1	4(16)	0	0	0	0
TLC-DE	0	0	0	0	1	0	0	1(4)
PLT-DE	0	0	0	0	1	0	0	1(4)
Anemia	0	1	1	2(8)	1	0	0	1(4)

Abdominal fullness and decreased appetite in our study was present in 62% and 32% cases respectively. This was slightly higher when compared to the study by Kumar *et al*., [5]. Pain abdomen and weight loss was seen in 30% and 18% cases respectively, which was slightly lower when compared to the study by Kumar *et al*., [5] Joint pain and weakness was seen in 2% and 34% cases which was much lower when compared to the study by Kumar *et al*., [5]. Weakness in our study was comparable to that of Singh *et al*., [12] Our study was completely in discordance with the international study done by Savage *et al*., [11] In this study, most common feature was weight loss (20%). This can be explained by fact that in western countries, symptomatic patients as well as patients selected on screening bases are included in the studies.

In our study, splenomegaly and anemia was seen in 100 % cases which was same as in Ghalaut *et al*., study [13]. In other Indian study, splenomegaly and anemia ranged from 95.25 to100% and 88.5%-100% respectively. In Savage et al study, splenomegaly was seen in 75.8% cases [11].

Hepatomegaly and Lymphadenopathy was seen in 38% and 2% cases which was low as compared in Indian study. In international study, hepatomegaly was seen in 2.2% cases only which were comparable to our study.

There was improvement in physical signs and symptoms in both groups after treatment. This was in agreement with Ghalaut *et al*., [13].

In our study, out of the 5 patients in accelerated phase, 3 patients (60%) achieved complete hematological response while out of 47 patients in accelerated phase in Deshmukh *et al*., study, 26 patients (55.3%) achieved complete hematological response [4].

In our study 3 patients of imatinib group and 2 patients of hydroxyurea had CHR. p value was not significant. Thus both drugs can be used to obtained hematological response in CML-AP. Yet imatinib is a better choice in CML-AP when compared to hydroxyurea.

4 patients in imatinib group and 3 patients in hydroxyurea group were on continuous therapy in CML-AP. While 1 patients of imatinib group and 2 patients of hydroxyurea group were on dis-continuous therapy in CML-AP.

Table-4: Hematological and cytogenetic responses in CML-BC in Indian and International studies

Author	Place	Year	No of Pt	CHR n (%)
Sawyers *et al*., [14]	USA	2002*	229	52%
Kantarjian *et al*., [15]	USA	2002*	75	52%
Deshmukh *et al*., [4]	India (Mumbai) India (Varanasi)	2001-2003	47	11(36.7%)
Present study		2000-2011	IM-5 HY-5	3(60%) 1(20%)

*year of publication

In our study, out of 5 patients 3 (60%) achieved a complete hematologic response with imatinib while in Deshmukh et al study, out of 30 patient, 11 (36.7%) patients achieved a complete hematologic response [4].

In the international study by Sawyers *et al*., in 2002, on 260 CML patients in blast crisis and Kantarjian *et al*., in 2002 on 75 patient complete hematologic responses was seen in 52% [14, 15]. Due to small sample size it was difficult to comments on

comparability. In our study we found 3 (60%) patients in Imatinib therapy and 1 (20%) patients in hydroxyurea therapy had CHR. Thus Imatinib is the better choice in treating CML-BC.

The side effects of Imatinib in our study were comparable to that of Kumar *et al*., [5]. The response rate and toxicity profile in our patients appears to be different. It is possible that Indian population handles Imatinib differently. Imatinib is metabolized in the liver by cytochrome enzyme system. There may a genetic polymorphism for this enzyme in the Indian population, which may result in different pharmacodynamic profile. Dietary factors, additional non-conventional remedies and alcohol may induced the cytochrome enzyme system and alter the metabolism of imatinib. Last but not the least, important is the compliance of the patients, which may have bearing on the ultimate response.

In our study, the drug - Imatinib mesylate was found to be superior to hydroxyurea as in Ghalaut *et al*., study [13].

In order to evaluate which drug is better, further conventional cytogenetic and molecular study is needed. Hence it is immensely important and desirably to improve conventional cytogenetic study owing to lack of which further evaluation of response to treatment of drug was not possible.

CONCLUSION

Imatinib mesylate, a selective inhibitor of the protein tyrosine kinase has shown promising results in chronic myeloid leukemia in all phases. Its efficacy, specificity and the safety profile makes it a strong contender for the first line therapy in CML.

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Abbreviations

CML- Chronic Myeloid Leukemia
CP-Chronic Phase
AP-Accelerated Phase
BC-Blast Crisis
TLC- Total Leukocytes Count
PLT - Platelet count
HB - Hemoglobin
SP-Spleen
CHR-Complete Hematologic Response
PHR - Partial Hematologic Response
HY- Hydroxyurea
IM –Imatinib Mesylate

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