Original Article-III

Imatinib Mesylate in Newly Diagnosed Patients of Chronic Myeloid Leukemia

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is most common leukemia among adults in India and accounts for 30% to 60% of all adult leukemias. Imatinib mesylate induces the highest rate of complete hematological and cytogenetic responses. We evaluated the efficacy and safety of imatinib, in newly diagnosed patients of chronic phase CML.

Methods: One hundred newly diagnosed patients of CML-CP were enrolled. Patients received imatinib 400mg orally daily and were monitored carefully for any adverse effects. Bone marrow cytogenetic studies were repeated at 6 months to ascertain the response. In patients not achieving a major cytogenetic response, (MCR) the dose of imatinib was increased to 600mg daily.

Results: Imatinib produced Complete hematological remissio in 90% of the patients, 50% achieved a MCR at 6 months and 55% at 12 months. The drug was generally well tolerated.

Conclusion: Lower cytogenetic response rates to imatinib in the present study needs further evaluation.

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INTRODUCTION

Chronic myeloid leukemia (CML) is the commonest leukemia among adults in India. Its incidence varies from 0.8 to 2.2 per 1 lakh population in males and 0.6 to 1.6 per 1 lakh population in females accounting for 30 to 60% of all adult leukemias.[1] Imatinib mesylate, a specific inhibitor of BCR-ABL tyrosine kinase has dramatically changed the management of CML. Of all non-transplant therapies imatinib induces the highest rate of complete hematological (CHR) and cytogenetic responses.[2] The major end point in patients treated with imatinib is major cytogenetic response (MCR, Philadelphia chromosome positive metaphases of 34% or less). Achievement of a MCR at 3, 6 or 12 months is associated with an improvement in overall survival.[3] Patients with a MCR are less likely to relapse and most patients who achieve a MCR do so within six months of therapy.[4] Two single centre experiences from India on the use of imatinib in the treatment of CML have shown somewhat similar results.[5, 6] While complete hematological response (CHR) achieved in the two studies was comparable to Western data, MCR and complete cytogenetic response (CCR) were lower. Both studies had included newly diagnosed as well as previously treated patients. Present study was undertaken to evaluate the efficacy and safety of imatinib mesylate, only in newly diagnosed patients of CML-CP and to

compare the results obtained with those reported in literature.

METHODS

Between June 2003 and October 2005. 100 newly diagnosed patients with Ph+ CML-CP were included in the study. Eligibility criteria included-age 15 years and older, Eastern Cooperative Oncology Group-(ECOG) performance status of 0 to 2, adequate hepatic and renal functions, no prior imatinib therapy, non pregnant patients. CML-CP was defined as less than 10% blasts and less than 20% basophils in the peripheral blood and bone marrow and a platelet count of more than 1 lakh, but $\leq$ 10 lakhs/cmm.[7]

Therapy was initiated with imatinib 400 mg orally daily and patients were monitored carefully for any adverse effects. Complete hemogram and liver function tests were done once in two weeks during the first month and there after monthly. Toxicities encountered were graded as per the National Cancer Institute common toxicity criteria version 2. Both hematologic and non-hematologic toxicities were managed with short interruptions of treatment and supportive measures, but the daily dose of imatinib was not reduced below 300 mg/ day. Therapy was discontinued with severe extramedullary toxicities. Marrow studies including morphology and cytogenetics were performed every 6 months. In patients not achieving a MCR at 6 months, dose of imatinib was increased to 600 mg/day and therapy continued.[2]

RESPONSE DEFINITION:

Complete hematologic remission (CHR) was defined as WBC <10,000/mm^3, platelets <4.5 lakhs/mm^3, no immature peripheral cells and disappearance of all signs and symptoms of disease including splenomegaly, lasting for at least 4 weeks.[8]

Cytogenetic response was defined as

- Complete – no Philadelphia (Ph) chromosome positive metaphases
- Partial – 1-34% Ph+ metaphases
- Minor - 35-90% Ph+ metaphases
- No response – 91-100% Ph+ metaphases

At least 20 metaphases were analyzed for a cytogenetic response evaluation.

RESULTS

Patient characteristics are shown in Table 1 and response to imatinib therapy is shown in Table 2.

Median time to achieve CHR was 1 month. ranging from 2 weeks to 3 months. Median time to cytogenetic response was 6 months (First cytogenetic response assessment done only after 6 months of therapy) Treatment was discontinued in one patient due to severe skin reaction. Of the remaining 9 patients who failed to achieve a CHR, three progressed to accelerated phase (AP) within 6 months and rest progressed within 1 year.

Toxicities to imatinib therapy are shown in Table 3.

DISCUSSION

In the present study, although imatinib produced CHR in 90% of the patients, only 50% achieved a MCR at 6 months and 55% at 12 months as compared to the 86- 87% reported in major trials involving newly diagnosed patients of CML-CP.[9, 10] (Table 4)

Adverse events with imatinib were similar to those reported in other trials.[9, 10] Fluid retention was the commonest side effect, which responded to low dose diuretics. Skin reactions were managed with corticosteroids and

Table 1: Patient Characteristics

Age, (years)		Platelet count	
Median	32	≥ 4.5 lakhs/mm^3	59
Range	15-73	< 4.5 lakhs/mm^3	41
Sex	Number of Patients	Peripheral blasts	
Males	56	Present	100
Females	44	Absent	00
Duration of symptoms		Marrow blasts	
Median	3 months	≥ 5%	44
Range	2wks-1year	< 5%	56
Hemoglobin		Cytogenetics	
< 12g/dL	93	Typical	93
≥ 12g/dL	07	Variant	07*
WBC count			
= 50,000/mm^3	95		
< 50,000/mm^3	05		

*Variant cytogenetics included two simple t (2; 22) and t (4; 22) and five complex translocations t(15; 19; 22); t(1; 9; 22); t(9; 18; 22); t(9; 11; 22) and del(9) t(9; 22).

Table 2: Response to Treatment

	6 months	12 months
CHR %	90	90
MCR %	50	55
CCR %	30	38
Minor CGR %	05	05
No response %	41	30
Progressive disease %	03	09

CHR -- Complete hematological remission MCR -- Major cyto genetic response CGR -- Complete cyto genetic response

Table 3: Common Adverse Events to Imatinib Mesylate

Superficial edema & weight gain	43%
Skin rash	35%
Musculoskeletal pain	15%
Gastro intestinal (Vomiting, diarrhoea)	12%
Neutropenia	
Grade 3	11%
Grade 4	05%
Thrombocytopenia	
Grade 3	07%
Grade 4	00%

*Only one grade 4 non-hematological toxicity, (grade 4 skin rash) was seen.

Table 4: Imatinib mesylate in newly diagnosed patients: Review of Literature

Study	No. of patients	CHR	MCR	CCR
S'O'Brien et al[9] Median follow up (19 months)	1102	95.3%	87.1%	76.2%
Kantarjian et al[10] Median follow up (9 months)	50	98%	86%*	68%*
Desmukh et al[6]	24	100%	62.5%	41.7%

*Results with conventional cytogenetic studies alone. CHR -- Complete hematological remission MCR --Major cyto genetic response CCR-Complete cytogenetic Response

Table 5: Comparison of patient characteristics between three studies:

Parameters	Present study	Kantarjian et al[10]	S'O'Brien et al[9]
Hemoglobin	< 12g/dL 93%	< 12g/dL 38%	Median - 13g/dL
WBC count	> 50,000/mm^3 95%	≥ 50,000/mm^3 22%	Median - 17,900/ mm^3
Platelet count	> 4.5 lakhs/ mm^3 59%	≥ 4.5 lakhs/mm^3 34%	Median - 3.36 lakhs/mm^3
Peripheral blasts	Any 100%	Any 28%	Median - 00%
Marrow blasts	> 5% 44%	≥ 5% 00%	

interruption of treatment, except in one case where the drug had to be discontinued permanently. Musculoskeletal pain responded to analgesics. The drug was safe and well tolerated. There were no deaths due to toxicity.

The study by Desmukh et al from India, also report a low MCR of 62.5% in patients of early chronic phase CML.[6] The consistent finding of a lower cytogenetics response rate to imatinib in Indian patients from these different studies, points to the need for further investigation and research in this field.

What could be the possible reasons for these inferior results? (i) Late present ation could be one possiblility (table-5). In the present study more than 90% of patients had Hb <12 g/dL and WBC > 50000/mm^3; about 60% had platelet count >4.5 lakhs/mm^3 and all patients had peripheral blasts about 4-5% with > 5% blasts in the bone marrow. (ii) Lower plasma levels of imatinib may be associated with lower cytogenetic response. Could there be lower plasma levels of imatinib in our patients population as has been reported recently in a study from India.[11]

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