Original Article (I)

Therapy with Imatinib Mesylate for Chronic Myeloid Leukemia

BRIJESH ARORA, LALIT KUMAR, MAMTA KUMARI, ATUL SHARMA, JYOTI WADHAWA AND V KOCHUPILLAI

ABSTRACT

BACKGROUND :

The tyrosine kinase inhibitor, STI-571 (Imatinib mesylate, Gleevec) has been introduced recently for the treatment of chronic myeloid leukemia (CML). We analysed the results of 118 CML patients treated prospectively with Imatinib. We also compared the results of 79 chronic phase CML patients treated with Imatinib to those with 114 similar patients treated with interferon-μ (IFN-μ).

PATIENT AND METHODS :

Patients median age was 38 years , ranging from 13 to 65 years. There were 84 males and 34 females. 79 patients were in chronic phase (CP) , 23 accelerated phase (AP) and 16 were in blast crisis (BC) at the time of treatment. 62 patients (CP - 48/79 and advanced CML 14/39) were pre-treated with IFN-μ alone , 43 with hydroxyurea alone, 4 with stem cell transplantation (allogeneic-2, autologous-2) and one with busulfan alone. Imatinib daily dose ranged from 400 mg for chronic phase to 600 mg for patients with advanced CML. Median duration of Imatinib therapy was 6 months, ranging from 1 to 27 months.

RESULTS

Chronic Phase : 96% of patients achieved complete hematologic remission (CHR) at a median interval of 3 weeks. Major cytogenetic response (CGR) rate was 30% and occurred at a median interval of 5 months. Advanced CML : CHR and major CGR rates were 35% and 20%, respectively and median time to achieve response was 34 days and 9 months) , respectively. Weight gain, fluid retention, skin rash, nausea were common grade I-II non-haematological toxicities. Grade III-IV neutropenia and thrombocytopenia were seen in 16% & 10% of patients, respectively. A total of 19 patients have died; 14 in the advanced CML group due to progressive disease, 5 in the chronic phase group, 4 of progression to blast crisis and one of bone marrow aplasia and its associated complications.

Comparison with IFN-μ : CHR rates (96% vs 31.6%) and median time to achieve CHR (3 week vs 24 weeks) were significantly higher for patients with imatinib. Major cytogenetic remission rates (30% vs 30%) were similar but time to achieve major CGR was higher for imatinib group (5 months ((2-19 months) vs 6 months (3 to 12 months) . Five patients (5/79, 6.3%) developed progressive disease in the imatinib group compared to 19 (16.6%) in the IFN-μ treated group (BC-15, AP 4). Imatinib was stopped in one patient due to toxicity compared to two patients in the interferon group. One patient died of toxicity in the imatinib group, none in the IFN-μ group.

Department of Medical Oncology, Institute Rotary Cancer Hospital
All India Institute of Medical Sciences, New Delhi-110029
Brijesh Arora- Presently at Department of Medical Oncology
Tata Memorial Hospital Mumbai-400012
Correspondence to : **LALIT KUMAR**
E mail: lalitaiims@yahoo.com

CONCLUSIONS :

Present study confirms the findings in earlier reports that treatment with imatinib is associated with higher and rapid hematological and cytogenetic responses in patients with chronic phase CML. These results are superior compared to those obtained with interferon a.

INTRODUCTION

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of the pluripotent stem cell. The disease is usually characterised by insiduous onset of symptoms, progressive splenomegaly, marrow hypercellularity, anaemia, leukocytosis, and cytogenetically by the presence of Philadelphia chromosome (Ph) t(9;22)(q34;q11) in 90 to 95% of patients. In the formation of Ph chromosome, ABL proto-ocogene is translocated from chromosome 9(q34.1) on to BCR gene in chromosome 22 (q11.2). The resultant fusion gene BCR-ABL transcribes a chimeric 8.5 mRNA which in turn is translated in a novel protein of p210 kda termed as p210. This new protein encodes an abnormal tyrosine kinase which causes leukemia.[1-2] Recently, a new drug, called BCR-ABL tyrosine kinase signal transduction inhibitor 571 (STI 571, imatinib mesylate) has been introduced for the treatment of CML. Imatinib functions through competitive inhibition at the ATP binding site of the enzyme, which leads to the inhibition of tyrosine phosphorylation of proteins involved in BCR-ABL signal transduction.[3-4]

Druker et al were the first to report the effectiveness of STI-571 in a series of phase I & II study studies.[5-6] Most recently, O'Brien et al for the IRIS study have reported the results of a phase III study comparing STI-571 with IFN-μ plus low dose cytosine arabinoside.[7] Published data from developing countries is scanty. We here report our experience of treating 118 patients of CML with imatinib mesylate.

PATIENTS AND METHODS

Between Jan. 2001 and June, 2003, 118 patients of CML were treated prospectively with Imatinib mesylate. Patients characteristics are given in table-1 & 2. Eligibility criteria included- diagnosis of Philadelphia (Ph) chromosome positive CML with ECOG performance status- 0 to 2, normal liver and renal functions. . Patients age ranged from 18 to 65 years . Patients with abnormal liver and renal functions (more than twice of upper limit of normal) , ECOG performance status 3 to 4 and those with grade III-IV cardiac problems were excluded. Patients were defined to have chronic phase , accelerated phase and blast crisis as per the standard criteria.

Imatinib Dose and Monitoring : Patients with chronic phase CML received imatinib 400 mg daily and those with accelerated phase/blast crisis received 600 mg daily. Patients were seen weekly during the first month , 2 weekly during second month and then monthly . On each visit, detailed physical examination and weight record was done. Patients were evaluated in detail for any adverse reaction . Blood counts and differential counts were done on each visit, liver and renal functions were done 2 weekly during first 2 months , then monthly. Bone marrow examination with cytogenetic studies was done in all patients before starting imatinib treatment then at 3 months interval. Hematological remission and cytogenetic response was defined as per the criteria used by Druker et al.[5] Patients found to have complete cytogenetic response underwent FISH and PCR studies for BCR-ABL.

STATISTICAL ANALYSIS

Descriptive statistics like mean, standard deviation (S.D) and median were calculated. Chi-square test and t-test have been performed where over applicable. P value <0.05 has been considered as statistical significance level.

RESULTS

Among 118 patients, 79 had chronic phase , 23-accelerated phase CML and 16 were in blast crisis. 84 of 118 patients were males and 34 were females. Base line characteristics are given in table –1.

Table-1 : Patients Characteristics

Characteristic	CP	AP+BC
Age –median (range)	38(11-65)	36(13-60)
Splenomegaly >10 cm	46(58%) 5(6.4%)	34(89%) 24(61.4%)
Hepatomegaly	24 (30%)	29(84%)
Median interval since diagnosis	25 months (2-204)	37 months (0.5 to 120)
Mean Hb G% (range)	12.5 (6.1-17.4)	8.6 (2.8-12.4)
Mean WBC ($x10^3$/cmm)(range)	21.57 (2.19-189)	40.5 (2.11-318)
Mean Platelets ($x10^3$/cmm)(range)	3.55 (0.6-27.3)	3.31 (0.15-11.3)
Basophils % Mean (range)	4 (0-15)	10 (0-31)
PB Blasts % Mean (range)	1.14 (0-10)	18 (0-90)
BM Fibrosis Grade I-II III-IV	 20(25%) 10(12.5%)	 17(43%) 8(27%)
Ph Chromosome +ve <35% 36-65% 66-95% >95% BCR-ABL+ve	 4% 4% 20% 70% 1.3%	 0 0 5% 83% 12%
Prior Treatment Hydroxyurea / Busulfan Interferon (IFN-μ) IFN + Ara-C BMT others	 32% 43% 18% __	 48% 30% 5% 12.5%

PB-peripheral blood, BM-bone marrow, BMT-bone marrow transplantation, IFN-interferon, CP-chronic phase, AP- Accelerated phase, BC- blast crisis

Table-2 : Response to Imatinib Therapy

Response	CP (n=73)	AP+BC (n=37)
Hematological (CHR)	95.8%	35%
Median time to achieve CHR (Range)	21 days (7-122)	34 days(3-140)
Cytogenetic response (CGR)		
Complete	13(24.5%)	1(6.7%)
Partial	3(5.6%)	2(13.4%)
Minor	17(32%)	1(6.7%)
No response	16(28.55%)	6(40%)
Median time to achieve CGR (Range)	5 months (2-19 months)	9 months (5-12 months)

CHR - Complete hematological remission, CGR-Complete cytogenetic response

Chronic Phase (CP) : Patients median age was 38 years (range, 13 to 65 years). One third of patients (36%) had received hydroxyurea only and were IFN naïve. Four patients had relapsed following BMT (allogeneic –2 and autologous 2). The median duration of treatment with imatinib was 6 months (range, 1-28 months). The median dose was 400 mg. There was only one child who received 300 mg daily. 14 (20%) patients required dose modification ; this included dose reduction in 10 patients due to grade III-IV toxicities .

Response : Following imatinib therapy, 95.8% of patients achieved complete hematological remission (CHR) at a median time of 3 weeks. Overall cytogenetic response (CGR) occurred in 70% of patients – major CGR in 16 (30%) and minor in 40% of patients. 13 of 16 (80%) patients with major CGR had complete CGR. The median time to achieve major CGR was 5 months (range, 2 to 19 months). Molecular remission was assessed in 8 patients (by RT/ Real time PCR/FISH), 5 of 8 patients were in molecular remission. Three patients had relapsed; of these 3 had hematological relapse and had progressed to blast crisis, two patients had cytogenetic relapse.

ACCELERATED PHASE (AP) & BLAST CRISIS (BC)

Among 39 patients , 23 had accelerated phase, 16 had blast crisis (myeloid-9, lymphoid –2, extrameduallary-4 and biphenotypic-1). Pre-treatment characteristics are given in table-1. The median time from diagnosis to imatinib treatment was 37 months (range, 0.5 to 120 months). Imatinib dose was 600 mg daily in 32 patients and 7 patients received 400 mg daily.

Table-3 : Prior Interferon therapy vs Cytogenetic Response

Group	Complete CGR	Partial CGR CGR	Minor CGR CGR	Minimal	No Response	Total
Prior IFN Treated	9	2	14	5	10	40
IFN Naïve	4	1	3	0	5	13
Total	13	3	17	5	15	53

IFN- interferon , CGR- cytogenetic response

Dose changes were made in 12 patients (32%) either due to progressive disease (in 3 patients dose was increased or decreased in 9 patients due to grade III-IV toxicity.

Response : Overall 75 % of patients had hematological response, of which 35% had CHR (accelerated phase, 45%, blast crisis 20%). The median time to achieve CHR was 34 days. 60% of patients achieved cytogenetic response; major- 20% and minor in 40%. The median time to achieve CGR was 9 months (range, 5 to 12 months). 14 of 39 patients (AP 4/23, BC-8/16) have died due to progressive disease (blast crisis)- 12 , one due to portal hypertension and myelofibrosis and in another patient cause of death is not known.

Comparison with Interferon alfa (IFN - a)

We compared the data on 79 CML CP patients treated with imatinib to 114 patients in CP treated with IFN-a 2b (Shanferon) [8]. All patients in the IFN group were enrolled within 8 weeks of diagnosis and received IFN-µ 5mU daily subcutaneously. Patients age ranged from 18 to 62 years (median - 37 years) . There were 75 males and 39 females. 57% of patients responded haematologically; CHR-31.6% and partial –25.4%. The median time to achieve CHR was 6 months, ranging from 3 to 12 months. Major cytogenetic response was seen in 30% of patients; complete-1.8%, partial-28% (table-4) . The median time to achieve partial and complete cytogenetic response was 6 & 12 months, respectively.19 patients had evidence of CML progression (blast crisis (n=15, accelerated phase, n=4. Two patients refused for further treatment after initial 4 weeks due to IFN- a toxicity - bone pains and fever . The major toxicity to shanferon were : grade I-II fever (78%), fatigue (25.4%), and myalgia (52%). Other adverse reactions included skin rashes, itching, GIT and neurological. No patient died of IFN toxicity.

Currently, 95 patients are alive, 91 in CP and 4 with AP. Four patients were lost to follow up and all 15 patients with blast crisis have died of progressive disease at a median interval of 6.5 months (range, 1 to 15 months). Kaplan Meier probability of survival at 36 months is 76%.

Table : 4 Imatinib versus Interferon – Alfa for chronic phase CML : A Comparison

	Imatinib n=79	Interferon Alfa,n=114	P value
Median Age in years (range)	38(13-65)	37(18-62)	
Sex M:F	60:19	75:39	
Median interval since diagnosis	25 months (2 to 204 months)	2 weeks	
Overall Hematological remission (%) CHR PHR	95.8% 95.8% -	57% 31.6 25.4	<0.001
Median time to achieve CHR	21 days (7 to 122 days)	6 months (3-12)	
Major Cytogenetic remission (CGR) Complete Partial Minor	30% 24.5% 5.6% 32%	30% 1.8% 28% 9.6%	ns
Median time to achieve major CGR	5 months (2 to 19 months)	Complete-12 mon. Partial- 6 mon.	
Progression to blastic transformation	5(6.3%) BC-4, EMBC-1)	19(16.6%) BC-15, AP-4)	<0.02
Died of toxicity	1	0	
Withdrawn due to toxicity	1	2	

BC-blast crisis, AP- accelerated phase, EM-extramedullary

Toxicity

Non Hematological Toxicity(table-5)

The most common non hematological toxicities were – weight gain, peri-orbital edema, and skin changes. Median weight gain was 6.5 kg (range, 2 to 23 kg) with median time of onset of weight gain being 3 weeks and median peak time of gain being 6 months. In the chronic phase group , 6 (8%) patients had significant weight gain (>20% of body weight). Hypopigmentation was seen in 45% of patients. This was generalised in majority with few had only truncal and facial

Table-5 : Toxicity to Imatinib Therapy

Toxicity	CP %		AP+BC %	
	Any grade	Grade III-IV	Any grade	Grade II-IV
Nausea	68	-	30	-
Edema	48	1.3	49	-
Weight gain	53.8	7.8	45.8	-
Myalgia	27.8	-	29.8	-
Arthalgia	20.3		8.1	5.4
Headache	19.2	-	16.2	2.7
Dyspepsia	16.7		13.5	-
Cramps	16.7		13.5	-
Bone pains	11.3		2.7	-
Fatigue	11.3		29.7	-
Diarrhoea	4.2		10.8	2.7
Constipation	4.2		2.7	
Fever	11.3		5.4	-
Rash	11.3	2.8	16.2	5.4
Pruritis	5.6	-	10.8	2.7
Hypo-pigmentation	41.2		43.6	
Hyper-pigmentation	3.9		-	-
Paresthesia	4.2		-	
Sweating	2.8		-	
Anorexia	2.8		-	
Dysgeusia	2.8		-	
Cough	2.8		2.8	
Raynaud's phenomenon	-	-	2.7	
Delirium			2.7	
Anxiety			5.4	
Gynecomastia			2.8	

CP-chronic phase, AP-accelerated phase, BC-blast crisis

hypopigmentation. 3 patients had hyper-pigmentation with patchy macular patches mainly in a butterfly distribution in the cheeks while one had face and limb hyper pigmentation. Skin rashes were seen in 14 % of patients with or without itching, 2 patients had grade III –IV skin toxicity requiring stopping the drug on one of them. Conjunctivitis was seen in 4% of patients, mainly irritation and redness of eyes.

Biochemical Adverse Events : (table-6)

Mild to moderate increase in liver enzymes was most common abnormality, seen in 20% of patients. In 4 patients with marked rise in the liver enzymes, imatinib was withheld with return of the enzymes to normal levels. Therapy with Imatinib was resumed in all patients in normal doses except one who required dose reduction . Two patients had evidence of tumour

Table-6 : Hematological & Biochemical Toxicity to Imatinib Therapy

Toxicity	**CP**		**AP+BC**	
	Any grade %	Grade III-IV %	Any grade %	Grade-III-IV %
Anemia	32	5.6	30.7	5.4
Thrombocytopenia	98	15.3	59	10.8
Leukopenia	47	16.7	67.5	24.3
Decreased BM Cellularity	39	27.3	37.5	
SGOT/SGPT increase	23.6	5.6	10.8	2.7
Bilirubin	1.4		8.1	
Renal	1.4		2.7	
Uric acid	1.4		5.4	
Tumour Lysis	1.4	-	1.4	

Hematological Toxicity (table - 6)

Pancytopenia or mono or bicytopenia was seen in up to 60 % of patients, it was severe (grade III/IV) in 16 % of patients requiring interruption or reduction in the doses of imatinib therapy. Bone marrow cellularity was reduced in 60% of cases evaluated; 27% of these had significant reduction in the cellularity (>50%). One patient had prolonged bone marrow aplasia, she died of bilateral fungal pneumonia.[9]

lysis syndrome, one in each chronic phase and advanced CML category.

Infections

Two patients had herpes zoster infection. Three patients had tubercular infection; tubercular lymphadenopathy-1, pulmonary and bone tuberculosis-1, and pulmonary tuberculosis-1. One patient developed severe bone marrow aplasia and died of pulmonary mucormycosis.[9]

Current Status

Presently, 96 of 118 patients are alive - chronic phase-71 (90%) , advanced disease-25 (64%). 19 patients have died ; chronic phase -5 (4 due to progression to blast crisis and one due to bone marrow aplasia, advanced disease-14 (intracranial bleeding-11, CNS leukemia-1, portal hypertension-1 and cause was not known in one patient). Three patients have been lost to follow up in the CP group (table 7).

Table-7 Current Status

Status	CP(n=79)	AP+BC(n=39)	Total (118)
Alive, on therapy	69	25	94
Alive, off Imatinib due to toxicity	1	-	1
Alive, on alternative therapy	1	-	1
Died	5 BM Aplasia-1 Blast crisis-4	14 (IC bleed=11, CNS leukemia-1, Portal hypertension-1, unknown-1)	19
Lost to FU	3	-	3

DISCUSSION

Two unique features of imatinib mesylate therapy include - higher responses and rapidity of response. In the present study, almost all patients (96%) with chronic phase achieved complete hematological remission (CHR) at a median interval of 3 weeks. These results are similar to those reported in land mark papers by Druker et al [5] and by O'Brien et al.[7] Our study population was unique as it included – patients with chronic phase and advanced disease (accelerated phase + blast crisis), most patients had IFN-a with or without low dose cytosine arabinoside -C for more than a year. Lower CHR rates (45%) in advanced CML compared to chronic phase (95%) are possibly reflective of resistance to imatinib therapy.[10] Such a rapid haematological response (median time 3 weeks and 7 weeks for chronic phase and blast crisis patients) is not seen with IFN-a or hydroxyurea.[11]

We also assessed cytogenetic response by analyzing Ph chromosome positive metaphases at 3 months interval. Major cytogenetic response rate of 30% was achieved among chronic phase patients compared to 20% among patients with advanced CML. Druker et al[5] in the initial phase II study reported a major cytogenetic response rate of 31% among 54 CP patients treated with Imatinib in the doses of ³300 mg daily. Similarly, among patients with blast crisis,[6] major CGR occurred in 12% . In a study by Kantarjian et al [12] major cytogenetic response rate of 60% was achieved in IFN pre-treated chronic phase CML patients. Lower cytogenetic response rate in our study is possibly a result of (i) higher proportion of IFN pre-treated and resistant patients (ii) higher proportion of patients with intermediate and poor risk Sokal score (data not shown) (iii) and brief follow up, median follow up only 9 months, compared to 18 months in the study by Kantarjian et al.[12] It has been suggested that patients who achieve minor cytogenetic response after 3-12 months of imatinib therapy, have a high rate of major

(68-83%) and complete (34 to 54%) cytogenetic response after 6 months of imatinib therapy.[12] Thus, it is possible that with longer follow up many more patient in the chronic phase group may be converted to major cytogenetic response. Cytogenetic responses occurred as early as 4 weeks to 16 weeks. Major cytogenetic remissions are practically not seen with hydroxyurea and occur in less than 20% of patients receiving interferon - a.[11,13] Cytogenetic remission were seen more often in patients with shorter interval from diagnosis to onset of imatinib therapy . Further, patients with no prior IFN therapy appear to have higher cytogenetic response rates. Therefore, rightly, imatinib has become first line therapy for newly diagnosed patients with CML.[14-15]

Molecular studies were done in 8 patients; 5 of these patients had evidence of molecular remission by FISH and PCR study but others continued to remain positive . In our study, the favorable prognostic factors for cytogenetic response were : Hb >12 G%, peripheral blast counts <3%, interval from diagnosis to imatinib therapy <24 months, and WBC <12000/cmm on univariate analysis while WBC <12,000 /cmm was the only important factor on multivariate analysis. These observations are similar to earlier reports.[16-17]

In the present study, 4 patients had received imatinib for post transplant relapse; allogeneic –2 and autologous-2. Both allogeneic transplant recipients achieved cytogenetic response- complete – one and major (80%) in another, at a median interval of 3 months. Higher cytogenetic response rates with return of donor chimerism was reported in a recent study.[18]

Therapy with imatinib was tolerated well by most patients although mild (grade I-II) side effects were seen in two thirds of patients. Common non haematological side effects included- nausea , weight gain, pedal oedema, facial puffiness, myalgia , arthralgia, and head ache. Frequency of these side effects was similar to those reported in the studies by Druker et al,[5-6] O'Brien et al[7] and others.[12-13] Diarrhoea, vomiting, rash and cramps were relatively uncommon in this study compared to previous studies.

We also observed unusual side effects, these included - pigmentary changes, conjunctivitis, and gynecomastia. Pigmentary changes were mainly localized depigmentation, or generalised hypopigmentation in majority with onset between 2 weeks to 3 months of starting therapy. These were seen in 40/110 (36%) cases while hyper pigmentation was seen in 3/110 (2.7%) patients. It has been suggested that imatinib may cause inhibition of C-kit and its ligand stem cell factor (SCF) which have regulatory role in melanocyte development and survival.[19]

Skin rashes, dryness, pruritis and desquamation were noted in 3 (2.7%) patients. In one patient , imatinib had to be stopped due to severe desquamation of skin inspite low dose of steroids. A variety of adverse cutaneous reactions have been reported in two recent studies.[20-21] In a study by Valeyrie et al, among 48 of 54 patients experienced atleast one skin reaction. These reactions consisted of 36 rashes, 35 oedema and 22 pruritis. In 5 patients skin rash were severe and required temporary interruption of imatinib treatment in 3 patients.[21]

Five patients developed findings suggestive of conjunctivitis with increased lacrimation and redness. This side effect has not been reported earlier in CML patients but has been observed in GIST patients on imatinib.[22] This is possibly due to inihibition of C-kit, which is expressed in many skin and mucosal cells. Three patients in our study developed bilateral gynecomastia. Only one small study has previously reported gynecomastia in 7 of 38 (18%) patients, here all the 7 patients had reduction in free testosterone concentration in serum. It has been proposed that imatinib inhibits C-kit and PDGF receptors in testis which have important role in testosterone secretion by leydig cells.[23]

Among the biochemical changes, transaminitis was observed in 10% of cases, which was generally mild and reversible. Apart from above adverse reactions, renal failure and tumour lysis has also been noted.[24,26] Two patients in present study also had tumour lysis syndrome, one in each chronic phase and blast crisis.

Among the hematological toxicity, most common were thrombocytopenia and neutropenia, both seen in 55% cases each. These findings are similar to those reported in earlier reports. Imatinib treatment was interrupted in 29% and 40% of chronic phase and blast crisis patients, respectively at a median duration of 8 weeks and 5.5 weeks. The median duration of stoppage was 3 weeks and 2 weeks, respectively. In the two earlier studies, drug interruption was required in 35%, 52% and 47% of patients with CP, AP and BC, respectively.[5-7,16-17] It has been suggested that frequent interruption of imatinib may affect achievement of cytogenetic response adversely.[27] Whether G-CSF should be used for such patients, needs further study.[28] Two patients in our study had herpes zoster and another 3 had tuberculosis. Cutaneous infections have been noted in earlier studies also.[29] There donot seem to be an increased risk of infections in patients on imatinib.[26]

Another important finding following imatinib therapy was reduction in the bone marrow (BM) cellularity seen in 16/29 (55%) cases which was grade III-IV in 6 /29 (20%) of them. CML is typically characterised with hypercellular marrow with myeloid hyperplasia. This is in contrast to hydroxyurea treatment where BM continues to be hypercellular. Similarly, BM trephine biopsy in most patients on IFN - a therapy continue to remain hypercellular, though occasional cases of hypoplasia/aplasia have been reported.[30] One patient developed severe BM aplasia (<5% cellularity) and subsequent pulmonary mucormycosis. Severe BM aplasia has been reported occasionally. Patients with prior treatment with IFN - a or busulfan are at high risk. The reasons for decrease in the BM cellularity are not clear; possibilities include deficiency of normal bone marrow stem cells or bone marrow stromal damage due to extensive previous therapy e.g. IFN-μ . Prior treatment with IFN-μ has also been recognized as one of the risk factors for severe myelosupression in a study by Mauro et al.[31] Approximately 2% of CML patients treated with IFN-μ therapy may develop bone marrow aplasia.[30] IFN-μ given immediately after busulphan may aggravate the potential for bone marrow failure associated with busulphan. About one third of patients had grade III-IV myelofibrosis prior to imatinib therapy in the present study ; following imatinib there was a reduction in the myelofibrosis in most of them confirmed on reticulin stain. There was no correlation between reduction in BM cellularity or fibrosis versus cytogenetic response. These findings suggest that these changes are not merely due to eradication of Ph+ve hematopoiesis and reconstitution of normal (Ph) marrow.[32-33]

One patient with advanced CML (lymphoid blast crisis) achieved complete hematological remission after 4 weeks of imatinib. While being in CHR, both in blood and marrow, he relapsed in CNS 3 months later. It has been suggested that imatinib does not cross blood brain barrier. Thus, lower levels of imatinib in CSF may not protect against CNS leukemia.[34-35]

Present study confirms the high hematologic remission and cytogenetic response rates with imatinib mesylate in these previously treated CML patients. Cytogenetic response rates are superior and side effects are less in chronic phase, interferon naïve patients. High rate of relapse in patients with advanced CML after initial response is indicative of development of resistance to imatinib. Elucidation of possible mechanisms and strategies to counter resistance to imatinib would be possible areas of research in future studies.

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