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Hematological and cytogenetic responses to STI571 therapy in chronic myeloid leukemia

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ABSTRACT

Chronic Myeloid Leukemia (CML), a malignancy/ cancer of the white blood cells (leukocytes), where in there is excessive multiplication of myeloid stem cells within the bone marrow, is caused by the Bcr- Abl tyrosine kinase, the product of the Philadelphia Chromosome. The hallmark of CML is the Philadelphia chromosome, which is present in more than 95% of patients. Imatinib mesylate, formerly known as STI-571 is a selective inhibitor of this kinase. A total of 25 patients had received imatinib mesylate therapy formed the subjects of this study. Patients were evaluated for cytogenetic and hematologic responses. Imatinib has shown remarkable clinical activity in patients with chronic myeloid leukemia. This study indicated that STI-571 has shown higher response rates compared with other therapy.

Key words : Chronic Myeloid Leukemia, Philadelphia, STI-571.

INTRODUCTION

Chronic Myeloid leukemia (CML) is a malignancy/ cancer of the white blood cells (Leukocytes), where in there is excessive multiplication of myeloid stem cells with in the bone marrow. Chronic Myeloid leukemia was the first human disease in which a specific abnormality of the karyotype – the Philadelphia chromosome could be linked to pathogenetic events of leukemogenesis. Philadelphia chromosome – the hallmark of Chronic Myeloid leukemia, is present in more than 95% of patients.[1] This genetic abnormality generates a fusion oncogene, Bcr-Abl, which encodes a constitutively activated Bcr-Abl tyrosine kinase. In at least 90% of cases, this event is a reciprocal translocation termed t(9;22), which forms this particular chromosome.[2,3]

Chronic Myeloid leukemia is potentially curable with allogenic stem cell transplantation, but fewer than 30 percent of patients have suitably matched donors.[3,4,5,6] Treatment with interferon alfa can induce a complete Cytogenetic response in 5 to 20 percent of patients and result in longer survival than that achievable with chemotherapy. Patients in whom interferon therapy fails are usually treated with hydroxyurea, busulfan, etc. The rate of hematologic response with these second line agents is approximately 50%, but cytogenetic responses are uncommon.

Imatinib mesylate (Gleevec, Novartis, Switzerland), a white to off-white to brownish or yellowish tinged crystalline powder, formerly called STI-571, is a potent and selective competitive inhibitor of the Bcr-Abl protein tyrosine kinase.[7,8,9] Daily doses of 400mg or more of Imatinib induced hematologic responses in nearly all patients with chronic phase CML with minimal toxic effects. Activity was also Philadelphia chromosome – positive observed in some patients.

MATERIAL AND METHODS

a. Peripheral Blood Sample, Heparin, RPMI-1640, PHA(Gibco), Colchicine(Gibco), KCl (Qualigens), Carnoy's Fixative, Trypsin, Saline (Merck), Giemsa(Qualigens), Gleevec(Novartis).

b. Laminar Air Flow (Rescholar), CO_2 Incubator (Hear Cell), Centrifuge (Remi), Cyclomixer, Micropipette, Microscope (Olympus BX60).

Total twenty five cases were investigated and all the cases were already registered from Jawaharlal Nehru Cancer Hospital and Research Centre, Bhopal. A complete blood count and a differential blood count were obtained every fifteen days interval and cytogenetic analyses were evaluated every one-month interval. Heparinized peripheral blood samples were collected for cytogenetic analysis and transfer into 6 ml of RPMI-1640 media with the presence of mitogen. Cells were cultured, harvested and treated with KCl. Swollen cells were fixed, dropped onto a frosted slide and kept for ageing. Slide were then stained with giemsa (GTG banding performed and karyotyped) and observed under microscope (Olympus BX60).

Table 1

S.No	Details	STI571	Others
1.	Case studies	20	5
2.	Age (yrs)	47	48
3.	Sex (M/F)	14 / 6	4 / 1
4.	Time from Diagnosis	12 mnths	12 mnths
5.	Spleen Size (>10cm)	14	5
6.	Hb (g/dl)	12	11.8
7.	WBC (10^9/L)	10	3
8.	TPC (10^9/L)	12	4

Table 2

Case No	Fever	Spleenomegaly	Hb (gm / %)	TLC (Cumm)	Total Metaphase Count	Ph Shows	Others Abnormality
A1	-	+	11.4	7100	13	04	+
A2	-	+	12.7	5700	34	13	-
A3	+	+	11.0	14900	27	09	-
A4	-	+	10.7	5400	30	03	-
A5	+	+	9.8	14700	45	12	-
A6	+	+	13.2	9600	35	12	-
A7	+	+	11.7	27000	44	14	-
A8	+	+	11.6	8400	17	11	-
A9	-	-	8.0	4800	13	09	-
A10	+	+	10.5	6800	27	19	-
A11	+	-	6.0	245000	09	05	-
A12	+	+	13.4	18200	24	16	-
A13	+	+	12.4	7500	20	11	-
A14	+	+	10.3	10700	29	14	-
A15	+	+	12.4	10500	30	10	+
A16	-	+	11.0	55000	23	09	-
A17	+	+	11.3	56000	34	07	-
A18	+	+	10.8	13000	18	09	-
A19	-	+	8.2	4000	34	10	-
A20	+	+	12.4	8600	16	05	-
A21	+	+	10.8	4500	34	05	-
A22	+	+	12.8	6600	23	12	-
A23	-	-	9.8	16000	19	06	-
A24	+	+	12.3	5400	36	09	-
A25	+	I+	13.1	4900	23	02	-

RESULTS

Hematological/ Clinical features of Patients

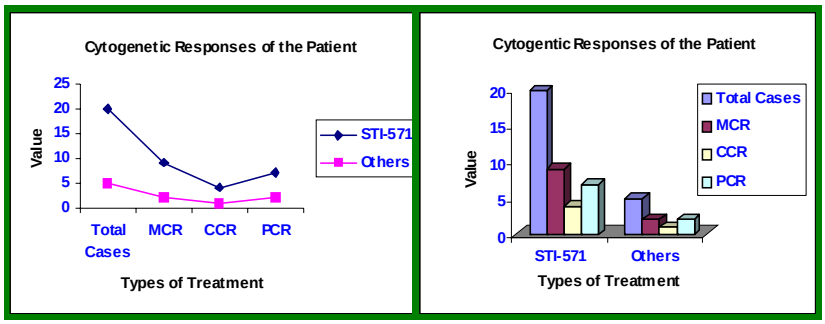
DISCUSSION

In the present study twenty-five cases (M: F = 21: 4) of chronic myeloid leukemia were studied. Their mean age was 32.8 (Range 06 years – 78

Table 3:

S. No	Response	STI-571	Others
1	Total Case Studies	20	5
2	Major Cytogenetic(MCR)	9	2
3	Com. Cytogenetic(CCR)	4	1
4	Partial Cytogenetic(PCR)	7	2

Cytogenetic Observation



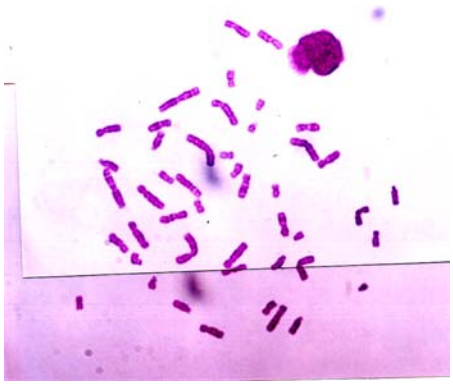


Fig. 1

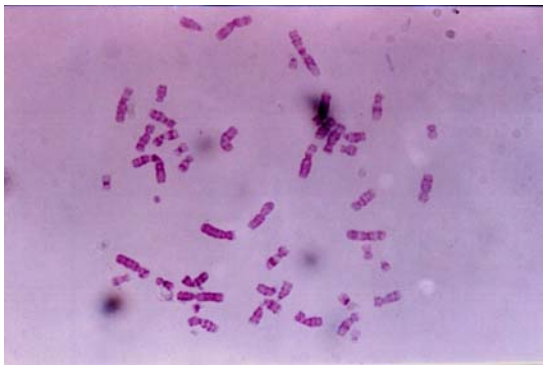


Fig. 2

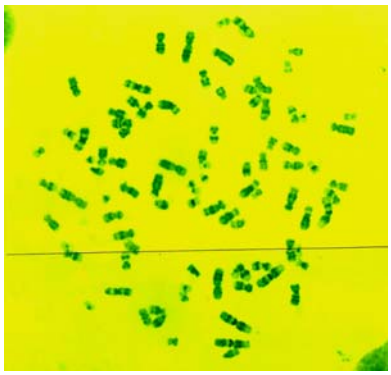


Fig. 3

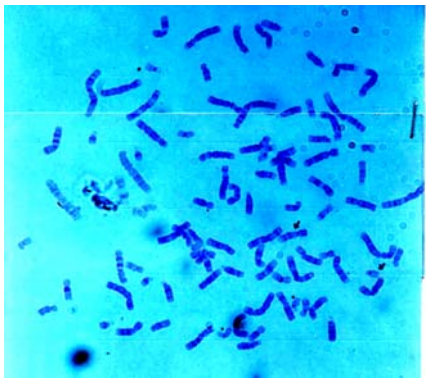


Fig. 4

years). Out of these twelve had a rural background and thirteen had an urban background. Details of their age and sex distribution, clinical features and laboratory investigations are shown in the table.

All the 25 cases of chronic myeloid leukemia included in this study were Philadelphia chromosome positive. Philadelphia chromosome was first described by *Nowell and Hungerford* (1960). It has also been reported by *Tough et al* (1961), *Fitzerald et al* (1963) and *Whang et al* (1963), that during remission induced by therapy when the Philadelphia positive cells in peripheral blood cultures are almost depleted, the percentage of abnormal cell line with Philadelphia positive chromosomes in bone marrow is hardly affected. Only two cases of CML had abnormal karyotypes i.e. in the form of Polyploidy and Fragments apart of the sole abnormality t (9; 22) (q34; q11).

Our results are similar with *Kemp et al*. (1964), who reported hyperdiploidy unrelated to Philadelphia chromosome but was found with the onset of the disease. STI-571 is a rationally designed, potent and selective inhibitor of the Bcr-Abl tyrosine kinase that has shown efficacy in all three phases of chronic myeloid leukemia. Imatinib induced better hematological and cytogenetic response than other therapy.

Since our study has been a small one, it is not possible to draw a clear- cut conclusion for which a larger data based study is required. Further it is felt that an attempt should be made to extend such studies to various family members of patients.

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