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RESEARCH ARTICLE

Study of Imatinib Mesylate Treated Patients sufferening from Chronic Myeloid Leukemia

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ABSTRACT

Chronic Myeloid Leukemia (CML) is also an attractive target for a rationally designed drug development programme and it was probably the first form of leukemia to be recognized as a distinct entity. In our present follow up study, taken normal healthy individuals, Interferon alpha, Hydroxyurea, Imatinib mesylate treated patient. The percentage response rate of interferon was 90% in which 10% have shown complete response, 30% with partial response and 50% with stable condition. The response rates in patients treated with Imatinib mesylate have shown 87.5%. The overall major cytogenetic response (MCR) was 2.5%, Complete cytogenetic response (CCR) was 77.5% and 7.5% in stable condition. This clearly demonstrates that Indian patients respond to this drug better than their foreign counter parts. This may be due to multiple reasons including food, cultural and geographical conditions. Indian people are known for more consumption of the species. Their food ingredients may be expected to be viding better health surveillance. The most notable finding was transformation of the accelerated phase and into the chronic phase in some patients. This follow up study supports the global view that the therapy with Imatinib mesylate may be continued unless resistance against it develops and it should be considered as the drug of first choice in CML.

KEYWORDS : Chronic myeloid leukemia, Imatinib mesylate induction, Blood Culture, Follow up Study

1. INTRODUCTION

Chronic myeloid leukemia (CML) was probably the first form of leukemia to be recognized as a distinct entity. In 1845, two patients were described as having massive spleenomegaly associated with leukocytosis, which seemed to be a novel entity not explained by the other causes of spleenomegaly, such as tuberculosis, that were already widely accepted in the 1840s.[6] In general the cause of Chronic Myeloid Leukemia (CML) is unclear, but high doses of ionizing radiation may be an etiologic factor.[7] The first important clue to its pathogenesis came only very much later, when in 1960 newly developed techniques for studying human cells in mitosis allowed Nowell and Hungerford to detect a consistent chromosomal abnormality,[9,10] later termed the Philadelphia (Ph1 , or just Ph) chromosome and identified as 22qi, in persons with this disease. In 1973, Rowley observed that the Ph chromosome resulted from a reciprocal translocation that also involved chromosome 9; the abnormality is now designated t(9;22)(q34;q11).[13] In the 1980s, the Ph chromosome was shown to carry a unique fusion gene, termed *BCR-ABL*,[15] the generation of which is now believed to be the principal cause of the chronic phase of Chronic Myeloid Leukemia (CML). Chronic Myeloid Leukemia (CML) is also an attractive target for a rationally designed drug development programme. Imatinib mesylate is a protein tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in Chronic Myeloid Leukemia (CML).

2. MATERIALS AND METHODS:

The Selective cases were already registered and diagnosed on the basis of bone marrow or hematological picture at Jawaharlal Nehru Cancer Hospital and Research Centre,

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Bhopal. For Cytogenetic the samples are mainly peripheral blood and bone marrow. The controls are those who were not diagnosed as cancer or any else disease. Comparative details are shown in the graph no 1.

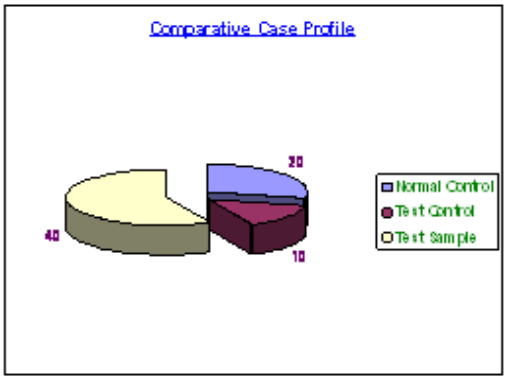

Fig 1: Comparative case profile

HAEMATOLOGICAL

Draw blood up to 0.5 mark of a WBC pipette. Carefully wipe excess blood outside the pipette by using fine tissue paper. Determination of differential count is useful to identify changes in the distribution of white cells which may be related to specific types of disorders. It also gives idea regarding the severity of the disease and the degree of response of the body. Blood smears also prepared immediately after skin puncture or vein puncture and fixed in methanol. After fixing, stained and observed under BX60 Olympus microscope.

CYTOGENETIC

1-2 ml of peripheral blood was drawn with a heparinized disposable needle and asceptically transfers into a sterile culture bottle with 5-6 ml of RPMI-1640 media containing L-Glutamine, Fetal Bovine Serum and Phytohaemagglutanin. The culture bottle was kept into an incubator for maintaining temperature and humidity for 72 hrs.

HARVESTING OF CULTURE

At 70 hrs, 50 microlitre, colchicine solution (Gibco, USA) was added as the pretreatment agent. After 72 hrs of incubation, the cell suspensions were poured into labeled centrifuge tubes and were centrifuged for 10 mins at 700-1400 rpm. Hypotonic solution (0.57% KCl) was added to the pellet of cells at the bottom of the tube which were suspended by the gentle flushing and kept at 37^0C for 45 mins.

The cell suspension was centrifuged again carefully at 700-1400 rpm for 10 mins and supernatant was removed. 6-8 ml of freshly prepared Caynoy's fixative was added and kept it for overnight at low temperature. Next day again centrifuge it and add freshly prepared Carnoy's fixative. Repeated this process 4-5 times. At last times, the fixative was removed and 0.5 – 1 ml of fresh fixative was added.

SLIDE PREPARATION

Slides were prepared by air drying techniques[12]. The cell suspension was gently flushed and 4-5 drops ere from a height of about 1.5 – 2 fts. Depending on the number of cells obtained, the suspension was concentrated by centrifugation and reduction of fixative. Four slides were prepared from each culture suspension and kept for ageing at 60^0C to study the GTG banding.

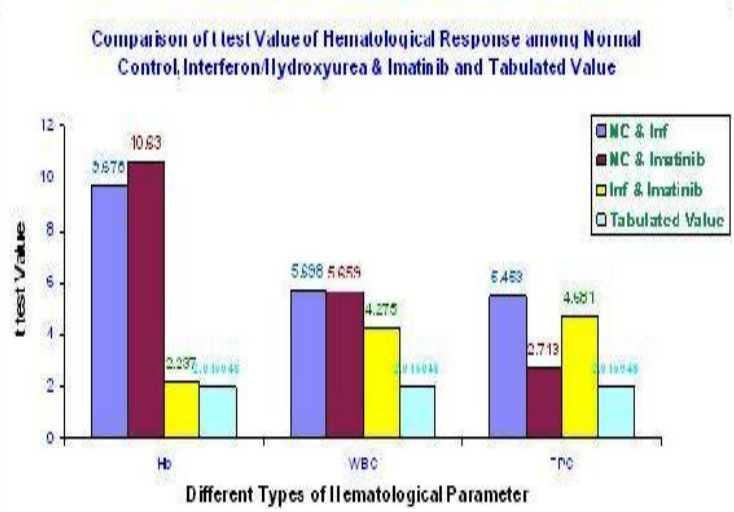

Fig 2: Comparison of t test value of Hematological Response

In this present study, three groups were taken to evaluate the haematological and cytogenetic variation in CML patients in India, Madhya Pradesh in particular. They were treated with Interferon alpha, Hydroxyurea, Imatinib mesylate.

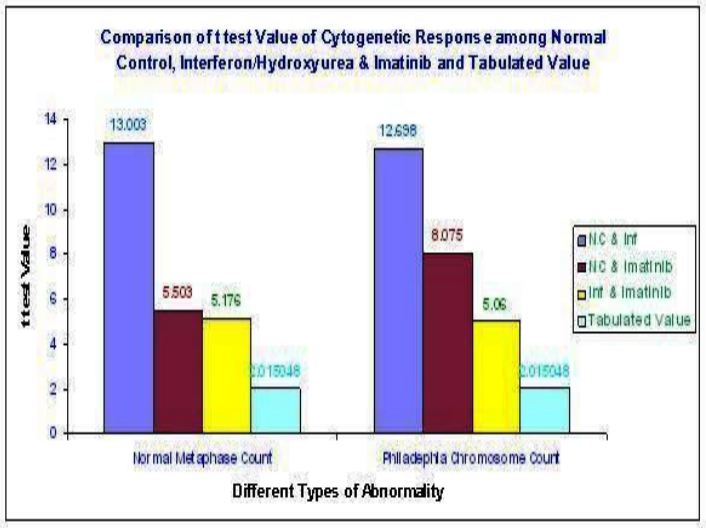

Fig 3: Comparison of t test value of Cytogenetic Response

Total 20 cases were screened under the normal control group that is without any treatment, the 10 cases were taken under the individuals clinically diagnosed as cancer patients treated with interferon alpha/ hydroxyurea and total 40 cases were screened under the individuals clinically diagnosed as cancer patients treated with

Imatinib mesylate. The comparative study of haematological values and cytogenetic values are mentioned in the graph no 2 & 3.

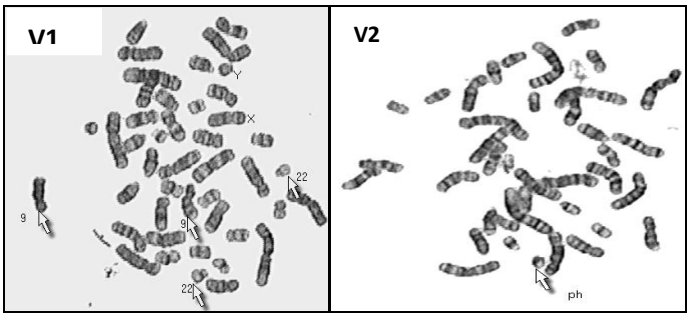

Fig No.4a & 4b: Microphotography Picture Plates showing Philadelphia (Ph) Chromosome in the First Visit (V1) & after Imatinib therapy revealed Normal Metaphase in the Visit Six (V6).

Philadelphia chromosome found in most of the cases in first visit and in last visit (V6) it was found normal, few others also found in some of the cases.[Figure no 4(a,b)].

4. DISCUSSION:

Imatinib has substantial activity and a fovourable safety profile when used as a single agent in patients with CML in blast crisis.[14] Complete haematological responses typically occurred within four weeks after the initiation of therapy.[3-5] In the present study, we have taken ten (10) patients in Interferon arm and forty (40) patients in Imatinib arm, out of which one (10%) were Interferon resistant and five (12.5%) were Imatinib resistant.

The cytogenetic response rates were higher than those reported in patients with Interferon. The percentage response rate of interferon was 90% in which 10% have shown complete response, 30% with partial response and 50% with stable condition. The response rates in patients treated with Imatinib mesylate have shown 87.5%. However, the overall major cytogenetic response (MCR) was 2.5%, Complete cytogenetic response (CCR) was 77.5% and 7.5% in stable condition. This was higher than the earlier reports where the response rate was 56.5%.[11]

This clearly demonstrates that Indian patients respond to this drug better than their foreign counter parts. This may be due to multiple reasons including food, cultural and geographical conditions. Indian people are known for more consumption of the species. Their food ingredients may be expected to be viding better health surveillance. Many of the active ingredients of there species are now established as an anticancer agent, for example, Curcumin, one of the most common ingredients of Indian food.[1,2,8,16]

Our study includes the relatively less number of patients because of a long term follow up criteria belonging to all phases of the disease. More or less, haematological and cytogenetic response has been remarkable as compared to the same study elsewhere. The most notable finding was transformation of the accelerated phase and into the chronic phase in some patients. There observations are adequately supported by the research finding elsewhere.

Imatinib mesylate is highly effective in the treatment of chronic phase CML and so it should be considered as the drug of first choice in CML. Our study supports the global view that the therapy with Imatinib mesylate may be continued unless resistance against it develops. In such resistant cases long term combination therapy may need to be evolved.

5. CONCLUSION:

This investigation was based on the years of follow up study of patients suffering from myeloid series of leukemia that is CML. The noteworthy observation was that the maximum number of CML cases in chronic phase was almost completely remitted. The accelerated phase was transferred to chronic phase due to the treatment. The chronic phase and accelerated phase was characterized by decreasing the total number of WBC count and by increasing the Hb content. As compared to similar results, our observation has been quite appreciable. This may be because of the fact that ethnic groups of this subcontinent differ from those in other parts of the world. It may also be due to the fact that a long term follow up study was carried out by us. It was, however, a concern for us that in about 12.5% patients resistance against this drug was observed, which is of course, in line with the results obtained elsewhere with more than about 40% resistance. It is never the less important to note that even as they showed resistance they were in absolutely stable condition. The resistance may develop due to pleiotropism in the structure of the key table that is Bcr-Abl kinase. So, the best course is to develop new targeted drug. The combined therapy may also be a solution to the problem.

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Conflict of Interest: None Declared

