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CASE REPORT

A CASE REPORT: IMATINIB INDUCED HEPATOTOXICITY IN CHRONIC MYELOGENOUS LEUKEMIA

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ABSTRACT: 45 Year old female admitted with complains of Body Pains, Generalized Weakness, and Lethargy. On evaluation CBP suggestive of Leukocytosis, Blast cells present. Ultrasound suggestive of Hepatomegaly, Splenomegaly. Bone Marrow suggestive of CML-Accelerated phase, FISH: Positive for BCR/ABL rearrangement (variant loss of ABL/BCR on Derivtive9). Liver Function Test: Normal. Patient was started on Imatinib after getting FISH report. Initially the patient tolerated the drug well with few days patient developed deranged liver enzymes which was not due to infective or inflammatory cause, but the drug was the cause of the deranged liver enzymes. In many trials it has shown that imatinib is hepatotoxic. In 1.5 to 5.2 % of patients develops elevation of transaminases i.e. (grade 3 or 4). In patients who have developed hepatotoxicity the Imatinib dose decrease or stoppage may results in reduction of hepatic dysfunction.in less than 0.5 % of patient imatinib discontinuation was needed in view of hepatotoxicity not reducing even after dose reduction also. It is utmost important to know that imatinib causes Hepatotoxicity. So patients on imatinib should be close follow up for the complication.

KEYWORDS: Imatinib, Hepatotoxicity, CML, Chronic Myelogenous leukemia.

INTRODUCTION: Chronic Myelogenous leukemia (CML) is a disorder of myeloproliferative lineage. It is characterized by increase in granulocytic cell lines series proliferation and it does not lose the ability and capacity to differentiate. Peripheral smear suggestive of immature precursor cells, increased granulocyte cells and blast cells may be present.

It is characterized by a cytogenetic aberration consisting of a translocation reciprocal between the long arms of chromosomes 9 and 22; t (9; 22). Due to The translocation it results in a shortening of the chromosome 22.

There are 3 phases in Chronic Myelogenous Leukemia.

Chronic Phase: characterized by enlargement of spleen and increase in leucocytes, with fewer symptoms like joint pains fatigue, arthralgia. This phase is commonly presently in initial diagnosis of CML patient, nearly 85 % of diagnosis of cml presents in this phase. During this phase if medications are started this can control symptoms, complications resulting from leukocytosis, anemia, thrombocytopenia, and splenomegaly. Newer drugs are available which is aimed at delaying onset of blast phase or accelerated phase.

Blast Crisis: Criteria for blast crisis are:

- More than 20% lymphocytes or myelocytes in peripheral blood or bone marrow aspirate.
- Bone marrow biopsy demonstrating large clusters of blasts.
- Development of solid focus of leukemia in bone marrow i.e. chloroma.

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The manifestations of blast crisis are similar to acute leukemia. Despite the best of the treatment the survival is very short and poor. In two thirds of cases, the blasts are myeloid. In remaining one third of patients, it exhibits a lymphoid type. During this phase the chromosomal abnormalities are found and other translocation are also found.

Accelerated Phase: various criteria have been develop to identity this phase.

World health organization and MD Anderson cancer center has also provided various criteria for the diagnosis of the accelerated phase:

- Myeloblast (10 – 19 %) in peripheral blood and bone marrow.
- Platelet count less than 1 lakhs unrelated to treatment.
- Platelet count more than 1 lakhs not responding to treatment.
- New cytogenetic abnormalities apart from Philadelphia chromosome.
- Increase in WBC count not responding to treatment.
- Splenomegaly Increase in not responders to treatment.
- Basophils more than 20% in peripheral blood and bone marrow.

CASE REPORT: 45 year of female diagnosed as CML. She was admitted with complains of sever body ache, generalized weakness, lethargy, loss of appetite. History of fever on and off, No h/o of chills and rigors, No h/o of diurnal variation, No h/o of burning micturition, No History of Shortness Of Breath, known HTN on Amlodipine 2.5 mg, no previous history of, DM, CAD, nor Pulmonary Tuberculosis, nor Bronchial Asthma.

No history Of Jaundice, nor Vaccination recently.

No drug history, Occasional Consumes Multivitamin for generalized weakness, otherwise no other significant drug.

On Examination: Moderately Built, Moderately Nourished, No signs of Pallor, Icterus, lymphadenopathy, cyanosis, edema. Pulse: 84/min regular BP: 110/70 mm of Hg, Heart: Normal S1 S2 heard, no murmurs, Respiratory system: normal vesicular breath sounds. P/A Mild Hepatomegaly, Splenomegaly. CNS: No FND.

On Investigation: CBP: HB: 12.2 g/dl, PCV: 38.3 Vol %, RBC: 3.5 Mill/Cu mm, WBC: 81000, Diff. Counts: Neutrophils: 61, Lymphocyte: 07, Monocyte: 06, Eosinophil: 05, Basophils: 04, Band forms: 03 Metamyelocyte: 04, Myelocyte: 04, Blast: 06, Platelets count: 4 Lakhs/Cu mm.

Peripheral smear picture: RBC are Normocytic, Macrocytic, and Normochromic, Nucleated RBC 5/100, a few polychromatophils are seen, WBC showing over whelming, leukocytosis with shift to left. Mild Basophilia and a few circulating blast present, platelets are adequate.

Sr. Calcium: 10.2 (8.6 – 10.3), Sr Magnesium: 0.7 (0.6- 1.1), LFT: Total Sr. Bilirubin: 0.7 (0.3-1.2), Conjugated Sr. Bilirubin: 0.14(upto 0.2), Total Sr. Proteins: 6.9(6.0- 8.3), Sr. Albumin 4.3 (3.5 - 5.2) Globulin: 2.6, A/G Ratio: 1.7, SGOT: 30 (upto 35), SGPT: 19 (upto 40), ALP: 116 (30- 120). RFT: Blood Urea: 38 (13- 43), Sr. Creatine: 08 (0.6 – 1.2), Sr. Uric Acid: 5.7 (2.6 – 6.0).

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U/S Abdomen: Liver is Mild enlarged in sized with homogeneous echotexture, No focal lesion, No intra hepatic biliary dilatation. Gall bladder is physiologically distended, No Calculi, Normal wall thickness. Spleen: Moderately Enlarged. Pancreas: is normal is sized and echo pattern, PD not dilated. Aorta and IVC are normal. Both kidneys are normal in size, Contour and Echo pattern, collecting system is normal. Tiny calculus noted in upper pole.

Urinary bladder is well distended, No Calculi.

Uterus is normal.

Bone Marrow Examination:

Bone marrow aspirate: Peripheral blood: RBC: anisocytosis, with Normocytic Microcytic Hypochromic Red Cells with Macrocytes and few tear drop cells. WBC: shows leukocytosis with myeloid left shift and 15% of blast. Platelet: adequate.

Differentials of peripheral blood: Neutrophils: 57%, Band Forms: 03%, Metamyelocyte: 02%, **Myelocyte:** 02%, Blast: 15%.
Basophils: 01%, Monocyte: 04%, Eosinophils: 06%, Lymphocytes: 10%.

Bone Marrow Aspiration: Performed from Rt Iliac Crest, Aspirate is diluted with blood, Trephine imprints shows hemorrhagic background. Blast accounting for 18% of marrow nucleated cells. These blast are 3-4 times the size of mature lymphocyte with scant to moderate account of cytoplasm and occasional; blast showing Auer Rods. Megakaryocytes are occasional.

Differentials: Blast: 18, myelocyte: 03, metamyelocyte: 02, ban d forms: 03, neutrophils: 55, **Lymphocytes:** 14, Eosinophils: 03, Euthyriod: 02.
Impression: Peripheral blood and Marrow cytological features consistent with CML Accelerated phase.
FISH Analysis was done: Positive for BCR/ABL rearrangement (variant loss of ABL/BCR on Derivtive9) in 8% of cell examined.

In view of the CML – Accelerated Phase patient was started on Imatinib 600 mg/ day. Patient tolerated well during the start of the treatment. Patient was given symptomatic treatment for the body pains, generalized weakness. But patient started to developed jaundice after initiation of Imatinib in 2 weeks, liver enzymes derangement were gross, we worked up for the cause of infective, inflammatory, and obstructive causes, all were negative. Patient was stopped Imatinib on 22 day. The liver enzymes were settling down.

CBP	Day1	Day 12	Day 18	Day 20	Day 24
HAEMOGLOBIN	12	12.2	10.4	10.3	10.6
RBC	3.5	3.5	3.1	2.8	2.8
WBC	81, 000	64, 000	40, 600	29, 500	22, 400
NEUTROPHILS	61	66	73	74	79
LYMPHOCYTE	07	05	07	07	10
EOSINOPHILS	05	03	02	07	07
MONOCYTE	06	05	03	04	02
BLAST	06	05	10	05	02
PLATELET COUNT	4.0 Lakhs	2.6 Lakhs	1.7 Lakhs	1.7 Lakhs	1.2 Lakhs

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HBsAg: Negative, Anti HCV: Negative, HIV1&II: Negative, Anti LKM Antibody: negative, Blood for MP: Negative, Leptospira Serology: Negative, Cultures: Negative, ANA: Negative, Coombs test Direct &**Indirect:** Negative. Sr. Iron level, VitB12, Folic Acid levels: Normal Limits.

DISCUSSION: Imatinib mesylate inhibits bcr-abl tyrosine kinase, Tyrosine kinase enzyme is regarded as the cause of Philadelphia chromosome- positive Chronic Myelogenous leukemia (CML), Gastro-intestinal stromal tumors (GIST) [1-2]and other rare neoplasms (Dermatofibrosarcoma Protuberans) Imatinib [3-5]is used for treatment of CML in:

- Accelerated or chronic phase
- Blast crisis, and
- Advanced gastrointestinal stromal tumors.

Our patient was started on Imatinib after getting FISH report. Initially the patient tolerated the drug well with few days patient developed deranged liver enzymes which was not due to infective or inflammatory cause, but the drug was the cause of the deranged liver enzymes.

In many trials it has shown that imatinib is hepatotoxic.[6-7] In 1.5 to 5.2 % of patients develops elevation of transaminases i.e. (grade 3 or 4). In patients who have developed hepatotoxicity the Imatinib dose decrease or stoppage may results in reduction of hepatic dysfunction.in less than 0.5 % of patient imatinib discontinuation was needed in view of hepatotoxicity not reducing even after dose reduction also. It is utmost important to know that imatinib causes Hepatotoxicity[1]. So patients on imatinib should be close follow up for the complication.

Clinical Features:

- Nonspecific Symptoms: Tiredness, Fatigue, and Weight loss, arthralgia, sometime due to hyper metabolism patients may present with excessive sweating and low grade fever
- CML is insidious in onset and on routine analysis leukocytosis and enlarged spleen are found.
- Symptoms in these patients are due hepatomegaly or splenomegaly or both hepatosplenomegaly.

  The disease has 3 clinical phases,
  - During the chronic phase the disease is easily controlled;
  - Transitional and unstable course (Accelerated phase); and,
  - Finally, a more aggressive course (Blast crisis), which is usually fatal.
- Due to severe leukocytosis it may result in leucostasis which can involve multiple organs.

TREATMENT: Goals of treatment of Chronic Myelogenous Leukemia (CML) have changed markedly in the past decade. They are:

1. To achieve a hematologic remission (normal complete blood cell [CBC] count and physical examination [i.e., no organomegaly),
2. To achieve cytogenetic remission (normal chromosome returns with 0% Ph-positive cells), and, most recently,
3. To achieve molecular remission (negative PCR result for the mutational BCR/ABL m-RNA). The last is an attempt for cure and prolongation of patient survival.

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A new approach to treatment of Chronic Myelogenous Leukemia (CML) is to directly inhibit the molecular cause of the disease that is, using a protein-tyrosine kinase inhibitor that inhibits the bcr-abl, tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Ph chromosome translocation abnormality.

STI571 or Imatinib mesylate: Inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for BCR/ABL and fresh leukemic cells in chronic myelogenous leukemia (CML) that is positive for the Ph chromosome[7]

- Data show the next-generation TKIs (i.e. Nilotinib and Dasatinib) were more efficacious in inducing molecular remission compared to imatinib.
- Dasatinib has been associated with pleural effusions, whereas Nilotinib has shown to produce the hepatic dysfunction and prolongation of QT interval.
- In chronic phase of CML patient is initiated with 400mg/day imatinib. It induces hematological complete response and cytogenic high response.
- Patient with accelerated or blast crisis the efficacy of imatinib is poor.
- Resistance of Chronic Myelogenous Leukemia (CML) cells to imatinib due to
    1. Overexpression of BCR/ABL and
    2. Mutations of the abl gene.
- Resistance can be overcome by increasing the imatinib dose.

Adverse Effect: Most frequent are Nausea, Vomiting, Diarrhoea, Edema, and Muscle Cramps. Hematologic Toxicity: Cytopenia, neutropenia, thrombocytopenia. Hepatotoxicity

Hydroxyurea: is deoxynucleotide synthesis inhibitor. Initially every 2 to 4 week the blood counts are done and dose adjustment is done based on these blood cells. Most patients achieve hematologic remission within 1-2 months. This it causes short duration of myelosuppression. Maintenance with hydroxyurea rarely results in cytogenetic or molecular remissions.

Busulfan: It is alkylating agent, and it is used in leukocytosis apart from hydroxyurea. Busulfan produces prolonged myelosuppressive effects.
Potential complications in long term usage are increased pigmentation, pulmonary fibrosis, prolonged suppression of marrow.

Leukaphersis: Leukaphersis: it is done by cell separator which rapidly lowers the WBC counts only.
Indication:

- It is used when patient leucocytes count is more than 3 lakh cell/ μL.
- Hyperviscosity secondary to leucocytosis.
- Tissues infiltration secondary to leucocytosis.

Interferon alfa:

- It can be used in patients whose age is older enough for BMT.
- Patients who do not have matched marrow donor.

Interferon alfa is given at an average of 3-5 million IU/d subcutaneously after hematologic remission with hydroxyurea.

Every 3 to 6 months the cytogenetic response is assessed by in situ hybridization fluorescence, or karyotyping, which helps to count the percentage of Ph- positive in bone marrow cells.

After 1 to 2 years of interferon therapy the cells should be 100 % normal. In patient with MRD bcr/abl positive have to on maintenance dose till they have MRD.

Patient on this therapy for more than 3 months will obtain 70 % Cytogenetic improvement. There is gradual decline in Ph Positive cells.

BMT: is considered in young patients (<55 yrs.) who have a matched sibling donor:

- It is considered for people less than 55 years.
- Within 1 year of the diagnosis BMT is recommended.
- If BMT is done with unrelated donor, the mortality rate is 30 to 40% whereas if BMT is done with matched sibling donor the mortality rate is 10 to 20 %.
- Patients with MRD after transplantation will require maintenance therapy of interferon or T cell reinfusion from donor.

CONCLUSION: Patients of CML when started on Imatinib have changes of developing Hepatotoxicity. Close monitoring of the liver enzymes to be done. Some reports of acute liver failure has been shown with imatinib. Early detection of the complication prevents life threatening Complication.

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