CASE REPORT

CHRONIC MYELOID LEUKAEMIA IN A 14-YEAR-OLD CHILD: AN UNUSUAL CASE REPORT

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Chronic myeloid leukaemia is a myeloproliferative stem cell disorder characterized by dysregulated production and proliferation of myeloid cells. Hallmark of the disease is the reciprocal translocation between chromosome 9 and 22 giving rise to an abnormal chromosome known as Philadelphia chromosome. Approximately 15% of all leukaemias are chronic myeloid leukaemia with a slight male predominance. This is a case of a 14-year-old boy with no premorbid presented with 4 months history of fatigue and shortness of breath on exertion. On examination patient was vitally stable. On general physical examination there was pallor and sternal tenderness. On abdominal examination spleen was palpable with a size of about 8cm. Respiratory, cardiovascular and musculoskeletal examination was unremarkable. Complete blood picture showed leukocytosis, low haemoglobin and normal platelets. Erythrocyte sedimentation rate was 65 mm/hr. Liver function tests, Renal function tests, Serum electrolytes, Urine routine examination and c-reactive protein were normal. Chest x-ray and Electrocardiography was normal. Peripheral blood smear showed neutrophils 56% with 3% lymphocytes, 1% blasts and retic count of 0.5%. Bone marrow biopsy was suggestive of chronic myeloid leukaemia which was confirmed by FISH and Cytogenetic studies.

Keywords: Chronic myeloid leukaemia; Myeloproliferative disorder; Bone marrow biopsy; FISH

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INTRODUCTION

Chronic myeloid leukaemia is a neoplasm of adults or old age with mean age of presentation 55–65 years. It is very rare in age of less than 20 years with only 3% of overall cases. Core genetic abnormality of chronic myeloid leukaemia is the fusion of two genes BCR present on chromosome 22 and ABL1 present on chromosome 9 resulting in BCR-ABL1 fusion gene. There are three phases of disease progression if untreated Early indolent or chronic phase, Accelerated phase and Terminal blast phase. Patients usually present with constitutional symptoms and splenomegaly. BCR/ABL1 gene which is hallmark of the disease is usually detected by polymerase chain reaction of bone marrow and blood. Chronic myeloid leukaemia is extremely rare in children. This is one such case of chronic myeloid leukaemia who presented at an extremely young age.

CASE PRESENTATION

A 14-years-old, previously healthy and active male presented with fatigue, undue shortness of breath on exertion for 4 months. On examination patient was vitally stable. On general physical examination there was pallor and sternal tenderness. On abdominal examination spleen was palpable with a size of about 8 cm. Respiratory, Cardiovascular and Musculoskeletal examination was unremarkable. Complete blood count showed elevated white blood cells count of 122.50 $X10^{3/}$micro L, Haemoglobin 9.8g/dl and Platelets $161x10^{3/}$micro L, ESR 65mm/hour, reticulocytes 0.5%. Liver function tests, Renal function tests, Serum electrolytes, Urine routine examination and c-reactive protein were normal. Chest x-ray and Electrocardiography was normal. Peripheral blood smear findings were as follow; Neutrophils 56%, Myelocytes 35%, Metamyelocytes 01%, Lymphocytes 03%, Monocytes 01%, Eosinophils 01%, Blast 01%, Basophils 02%. Bone marrow biopsy showed increased cellularity, depressed Erythropoiesis, hyperplastic and left shifted Myelopoiesis, increased Megakaryocytes, Blast cells <5% suggestive of Chronic Myeloid Leukaemia (chronic phase). Fluorescence in Situ Hybridization (FISH) for confirmation of BCR/ABL1 oncogene was done which turned out positive for atypical BCR-ABL translocation. 168/200 (84%) cells were BCR-ABL positive with karyotype of nu cish (ABL, BCR) X2, (ABL con BCR) X1[168/200].

Cytogenetic study was done for presence of Philadelphia chromosome, where 20 cells were counted. All cells were positive for Philadelphia chromosome and there was translocation between chromosome 9q34 and 22q11.2. Result shows 46, XY, t (9;22) (q34; q11.2) [20].

Patient was started on hydroxyurea and imatinib with regular follow up.

DISCUSSION

Chronic myeloid leukaemia is the first and foremost myeloproliferative disorder in which an acquired chromosomal abnormality is identified the Philadelphia chromosome.[1] Philadelphia chromosome is produced by the transfer of genetic material between the long arms of chromosomes 9 and 22 giving rise to BCR/ABL1 fusion gene.[1] Chronic myeloid leukaemia is an exceedingly rare myeloid cell neoplasm in children of age less than 20 years with 0.7 per million per year children aged 1–14 years and 1.2 per million per year adolescents aged 15–19 years.[2]

The diagnosis and treatment of CML in children, adolescents and young adults is different in few aspects compared to that of older people.[3] The prognostic scoring system of CML is based on both clinical and hematologic parameters including spleen size, platelet count and percentage of blasts, eosinophils and basophils in peripheral blood.[4] Without treatment CML is fatal with course spanning over few months to many years and with most recent and novel agents approximately 20% of all patients with CML have very poor survival outcome.[4]

Chronic myeloid leukaemia in children varies in many aspects compared to that in adult including highly aggressive signs and symptoms, Philadelphia chromosome positive acute lymphoblastic leukaemia like BCR/ABL1 breakpoints and extremely high ratio of mutated cancer driver genes.[2] Children with CML who are positive for Philadelphia chromosome and BCR/ABL1 have aggressive presentation with massive splenomegaly, highly raised white blood cell count and highest blast cell percentage.[4]

Tyrosine kinase inhibitors invention has dramatically revolutionized the treatment course of CML improving survival outcomes in a way that life expectancy of a patient with CML is almost the same as that of a healthy person of same age.[1,2] Although imatinib has shifted the paradigm for CML substantially yet second generation tyrosine kinase inhibitors (TKI) Dusatinib and Nilotinib are now been increasingly used as fist line therapy especially for chronic phase CML due to their more rapid and deeper response.[5] Most of the recent research have shown that PEG-IF alpha when added to imatinib the speed and depth of molecular response is accelerated compared to imatinib alone.[1]

Dusatinib and Nilotinib were approved in 2017 and 2018 respectively by FDA as both first- and second-line agents in treatment of paediatric CML.[3] The goal of therapy in adults and children is almost the same except the added challenge of minimization of toxicity of TKI's in children for next 6–7 decades.[5] Long term adverse effects of TKI'S in growing children are not completely known till now but it is thought to be different from adverse effects of TKI's on adults.[3]

Growth retardation is one of the serious adverse effects of imatinib in growing children. Exact mechanism is unknown but it is postulated that inhibitory activity at non-BCR/ABL1 sites is the probable cause of adverse effect on growth in children.[6] Response to tyrosine kinase inhibitors in children is monitored by the parameters including regression of spleen size, hematologic, cytogenetic and molecular responses.[3] There is no proper data available regarding when to stop TKI's in paediatric population.[3] Till date the only proven therapeutic modality in children to gain complete lifelong remission and to prevent them from taking long term TKI's is Allogenic Bone Marrow Transplant.[5]

CONCLUSION

CML is although rare in children but is extremely aggressive neoplasm and once diagnosed should be treated promptly as it can prove fatal if treatment is delayed. What is the best approach for the management of CML in children needs further research and data so that to improve the survival outcome in paediatric population. Meanwhile, treatment decisions must be made on a case-by-case basis.

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