Pediatric Chronic Myeloid Leukemia: Case Report of a Disease with a Unique Biology

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Abstract: Pediatric chronic myeloid leukemia constitutes around 3-5% of all childhood malignancies. It is characterized by t(9;22) with BCR-ABL1 fusion and p210 transcript. A 9-year-old male child presented with hepatosplenomegaly, anemia, marked leucocytosis, basophilia, myelocyte metamyelocyte peak, and 4% blasts in the differential count. Leukocyte alkaline phosphatase score was reduced and p210 transcript of BCR-ABL1 was identified by a polymerase chain reaction. Bone marrow was hypercellular with increased granulopoiesis, dyspoietic megakaryocytes and grade III reticulin fibrosis. The patient was treated with imatinib and showed a hematological response within one month and has a stable disease for the last 24 months. Owing to lack of specific guidelines on management and monitoring of pediatric chronic myeloid leukemia, it managed according to the adult guidelines by European leukemia Net or National Comprehensive Cancer Network guidelines. Drug toxicities, effect on growth, vaccination, and fertility are pressing issues in management of pediatric chronic myeloid leukemia with current first-line therapy with tyrosine kinase inhibitors.

Key Words: Chronic myeloid leukemia, pediatric, BCR-ABL1, splenomegaly, imatinib

Introduction
Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm, which constitutes about 15% new cases of leukemia in adults. It is quite rare in children and constitutes of only 3-5% of all childhood malignancies.(1,2) CML is characterized by acquisition of Philadelphia chromosome (Ph) by the leukemic cells in adults and children alike. The molecular pathogenesis involves a balanced reciprocal translocation of genes between chromosomes 9 and 22. The ABL1 gene on chromosome 9 fuses with BCR of Chromosome 22 leading to expression of BCR-ABL1 oncoprotein, which is a constitutionally active tyrosine kinase and promotes leukemogenesis via upregulation of RAS, RAF, JUN, MYC and STAT kinases.(1) The disease is aggressive in pediatric age group, which could be attributed to a breakpoint in the Alu repeat region of BCR, similar to Ph-positive acute lymphoblastic leukemia (ALL).(3) Children with CML are exposure to tyrosine kinase inhibitors during their growth years leading to higher burden of morbidities, which can be different from those of adults, and require careful monitoring.(1,3)

Case Report
A 9-year-old male child came with complaints of low-grade fever and abdominal distention for one month. Examination revealed pallor, hepatomegaly (liver span - 10cm) and splenomegaly (14 cm on splenic axis). His height was 117 cm (on the 3rd centile) and weight was 17.9 kg (< 3rd centile). Blood counts revealed anemia (hemoglobin- 5.8g/dl) and marked leucocytosis (total leucocyte count- 433.2 x 10^3/µL). Differential counts showed a myelocyte- metamyelocyte peak (metamyelocyte: 08%; myelocyte: 17%); a blast count of 4%; and basophilia (4%) (Figure 1). Leukocyte alkaline phosphatase score was markedly reduced (Patient- 2/ control-120).

Bone marrow aspirate smears showed a metamyelocyte peak (34%), blast count of 4%; basophilia (12%); suppressed erythropoiesis, and dyspoietic megakaryocytes (Figure 2). Bone marrow biopsy showed packed marrow spaces with increased granulopoiesis, dyspoietic megakaryocytes, suppressed erythropoiesis, and grade 3 reticulin fibrosis (Figure 3). With the available clinical and laboratory data, a diagnosis of chronic myeloid leukemia in chronic phase (CML-CP) was made. A BCR/ABL1 translocation assay was positive with genomic breakpoint at e14a2 or b3a2 corresponding to p210. The final diagnosis of BCR/ABL1 positive CML-CP was made.

The treatment was started with Imatinib, hydroxyurea and allopurinol along with adequate transfusion support. The patient tolerated the treatment well and was discharged in two weeks. Hematological remission was seen in one month, and...
no relapse/disease progression was observed for a follow-up period of 24 months. Molecular testing for remission was not performed due to financial constraints.

Discussion

cML in the pediatric age group comprised of only 2-3% cases of newly diagnosed leukemias. It is rarely seen in age <1 year, and age-adjusted SEER incidence rate for the age group of 0-14 years is 1.4 per 1,000,000 for the year 2010-2014.(4,5) In India, the National Cancer Registry Program groups all childhood leukemia in a single group, hence there is no separate data for cML occurring in this age group. Chandra D et al.(6) in their study on pediatric cML in India, reported the peak prevalence in the age group of 15-17 years (66.7%) with a male preponderance. The prevalence rate in the age group of 4-9 years was only 7.8%. The clinical presentation is similar to adult cML with constitutional symptoms and hepatosplenomegaly. The I-CML-Ped Study reported a higher total WBC count (mean 250x10^9 /L), lower hemoglobin, and higher peripheral circulating blasts than the adults.(4,7) Similar results were also reported by Chandra D et al. (6) and Millot et al. (8) Most cases present in the chronic phase, and presentation in the accelerated phase is rare. Reports have documented the first presentation in blast crisis, and both myeloid as well as lymphoid blasts have been reported.(2-4,6,7) The present case is a 9-year-old male who presented with fever, hepatosplenomegaly, TLC of 433.2 x 10^9/L, peripheral smear blast percentage of 4%.

Fluorescence in situ hybridization (FISH) is the most common test employed for the detection of BCR-ABL1 fusion for the diagnosis of cML. Reverse transcriptase-polymerase chain reaction (RT-PCR) is used to detect the breakpoint and for quantification of the transcripts, which further serve as a baseline for disease monitoring. The b2a2 transcript of p210 is the common breakpoint in adult cML; in contrast, b3a2 is the common transcript seen in the pediatric age group.(3) The presence of b3a2 transcript of p210 explains the higher leukocyte count in pediatric cML cases and helps predict the response to imatinib therapy. The b3a2 transcript shows a better response to imatinib therapy than the b2a2 transcripts.  The present case too showed the b3a2 transcript of p210.(1,3,6,7,9,10)

The differential diagnosis of cML in pediatric age group includes leukemoid reaction and juvenile myelomonocytic leukemia (JMML). Leukemoid reactions show a high TLC but lack a myelocyte bulge. Toxic granulation and a normal or raised leukocyte esterase levels help to exclude a diagnosis of cML. JMML also presents with fever, hepatosplenomegaly and anaemia but lacks the hallmark Philadelphia chromosome of cML. The accelerated phase is very rare in pediatric cML and has a prevalence of only 1.9%. A pediatric cML in lymphoid blast crisis is difficult to distinguish from a Ph-positive ALL on morphology and immunophenotyping alone. The presence of myelocyte bulge, basophilia, spleenomegaly, and p210 transcript helps in differentiation as Ph+ ALL characteristically shows p190 transcript.(1,4,7,11)

The risk of tumor lysis syndrome precipitating in a pediatric cML is low; however, the patients managed with oral hydration, allopurinol and hydroxyurea until the diagnosis is established. Imatinib has shown to be an effective tyrosine kinase inhibitor (TKI) in paediatric age group with large trials showing up to 89% complete hematological response within three months and 97% event-free survival in 18 months. The common side effects of imatinib therapy include nausea, vomiting, diarrhea, muscle cramps, bone pain, and cytopenias. Hepatotoxicity is seen in about 7.5% cases.(4,12) The major drawback is the effect of imatinib on bone growth in the prepubertal period. It has been documented to cause bone resorption, and dysregulation of Vit D and phosphate metabolism. Puberty shows catch-up growth however; the bone density is adversely affected.

Long term therapy shows adverse effects on thyroid and other endocrine organs responsible for normal growth. Immunosuppression following a TKI therapy also puts the children at risk, as live vaccines cannot be given. Fertility is another area of concern with long-term imatinib therapy; it can cross blood testes barrier and reduce the sperm count. Female partners of males on TKI are not at risk of pregnancy related complications, however in female patients contraception is advised while on TKI therapy. Duration of imatinib therapy is one more grey area in pediatric cML; a relapse is seen when the patients stopped TKI following achieving remission. There are no separate guidelines to monitor the therapy in pediatric cML, the European leukemia Net or National Comprehensive Cancer Network guidelines available for adults are used to guide treatment. Monitoring is done by three monthly evaluation of peripheral blood BCR-ABL1 by quantitative PCR and response graded as optimal, warning or failure. TKI is discontinued in optimal response while the warning response needs close monitoring. In case of a failure, TKI is changed. Other TKI approved for use in pediatric cML includes dasatinib and nilotinib; however, large-scale data

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regarding their efficacy and toxicity is still under evaluation.(1,4,6,7,13,14)

Conclusion
Paediatric CML is a rare disease and shows considerable differences from adult CML in clinical presentations, disease biology, and outcome. The first-line therapy is TKI; however long term use in pediatric patients raises concerns over their effect on bone growth, endocrine organs, vaccination and future fertility. The present lack of data on the disease progression, outcome, and standard guidelines for disease monitoring makes the management decision difficult.

References