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Myeloid Blast Crisis in A 15 Years Adolescent Under Treatment for CML

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ABSTRACT

Background

Chronic myeloid leukemia is relatively a rare haematological malignancy to present during childhood. CML is classically staged into three progressive phases - chronic, accelerated, and blastic. Blastic phase is the most critical phase likely to be fatal within few months. However, most children (95%) present in the chronic phase and are managed with oral tyrosine kinase inhibitor weighing the risk benefit ratio of toxicities during and after the Hematopoietic Stem Cell Transplantation. The main aim of treatment is to hault the progression to blast crisis. We report a case of 15 years' adolescent presented with huge splenomegaly and leucocytosis with 100% BCR-ABL fusion gene positive managed with Imatinib. He developed myeloid blast crisis even being on regular therapy with imatinib within 18 months. He survived the phase with meticulous investigations and management. Here we highlight the importance of HSCT for the eradication of the disease process even in those who were considered TKI responsive.

Keywords: BCR-ABL positive; leukemia; myelogenous.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder which is characterized by the presence of the BCR/ ABL fusion transcript encoded by the Philadelphia (Ph) chromosome, a result of a reciprocal translocation between chromosomes 9 and 22.[1]Around 2-3% of children younger than 15 years and around 9% in between 15-19years suffer from CML.[2, 3] The incidence of CML being 0.6-1 cases per million in children less than 15years and 2.1 per million for 15-19 years.[4] CML is defined in three phases-chronic, accelerated, blastic phase. The blastic phase is defined as the presence of at least 20% blasts in blood or bone marrow or the presence of blasts in extramedullary sites. CML in chronic phase to blastic phase(CML-BP) transformation is seen in less than 5% of children.[5] This transformation has a worse prognosis as it behaves as acute leukemia in children.[6] CML blast transformation is usually of myeloid type in 70% of cases and lymphoid in 30%.[6] Stem Cell Transplantation (SCT) is the only known curative therapy for CML till date. However, weighing the risk of toxicities following the SCT to the available TKI (Tyrosine Kinase Inhibitor), TKI is preferred treatment. The unknown late effects with TKI therapy and the limited understanding regarding the role of SCT among the TKI responsive CML-CP pediatric patients still makes the treatment controversial.[2, 7-10] This study aims to highlight the phases of CML and to consider treating even the blast crisis phase which is considered fatal.

CASE REPORT

15 years male presented to B.P. Koirala Memorial Cancer Hospital, Chitwan with the complaints of gradually progressive abdominal swelling for 5 months, on and off fever with 2 episodes of nasal bleeding. He had normal birth and development history. Physical examination revealed pallor with massive splenomegaly (20cm) below left subcostal margin but no hepatomegaly and lymphadenopathy. His initial investigation showed leucocytosis (TLC-1,68,000), Anemia (Hb-7.1gm%) and PBS showed markedly increased count with marked shift to left. Further investigation with bone marrow aspiration showed myelopoiesis with increase in myeloid series with increase in precursor cells (Blast-5%, Myelocytes-24%,Metamyelocytes-15%, Band cells-13%,N-16%), BCR-ABL gene rearrangement showed BCR:ABL ratio:54.581% with p210(e13a2,e14a2, Major)BCR-ABL rearranged copy:558823.FISH showed t(9,22)BCR:ABL1 fusion 100% positive. (Figure1). He was discharged on Imatinib at a dose of 340mg/m2. He had regular follow up with regular monitoring of BCR-ABL (Table 1).

Table 1. BCR-ABL gene rearrangement, PCR quantitative.

DATE	P210 (e13a2, e14a2, Major BCR-ABL)	ABL Copy Number	Percentage Ratio	International Scale	Type of transcript detected
4/10/2023	558823	1023840	54.581	34.17	Major p210
11/6/2023	17101	152490	11.215	7.02	Major p210
5/26/2024	1180	3300344	0.357	0.22	Major p210
10/7/2024	109493	251605	43.518	27.24	Major p210

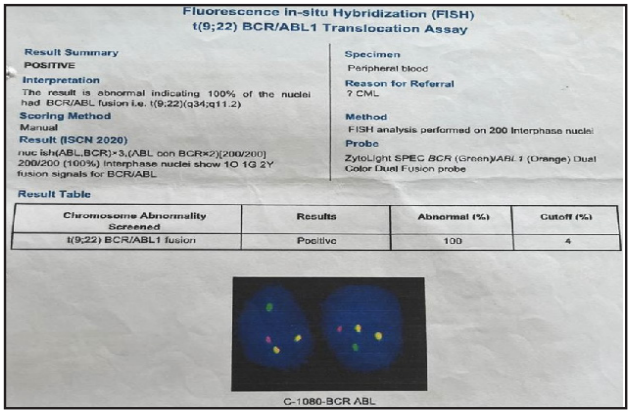

Figure 1. Fluorescence in-situ hybrixization (FISH).

He revisited OPD with complaints of fever after a period of about 18 months. Investigation revealed leukocytosis and Bone marrow suggested 70% blast, CML in blast crisis with transformation to acute leukemia. Immunophenotyping with flow cytometry showed CML in myeloid blast crisis. The positive markers were CD33, CD13, CD15, CD64, CD11c, CD4, CD36 and CD64 co expression, CD64 and CD11C co expression, CD36, CD38, CD123, HLA-DR, CD117, CD45. Karyotyping showed 47XY, t(9;22) (q34;q11.2), t(11;17) (q23;q21)t19(20). CSF

cytology was negative for blast. TKI sensitivity test was also positive. He was started on two drug chemotherapy. Cytarabine and daunorubicin during induction and high dose Cytarabine during consolidation. He had febrile neutropenia with pneumonia and perianal abscess during the treatment which was managed with no complications. After completion of the treatment, bone marrow evaluation was done which showed CML in chronic phase thus he was discharged on Imatinib. He was also counselled again for stem cell transplantation.

DISCUSSION

We report this case as a survivor of CML myeloid blast crisis, a condition often considered fatal within few months.[11] There are only a handful of cases who have survived CML blast crisis.[6, 12-14] The basic genetic abnormality noted in CML is a shortened chromosome 22 resulting from a reciprocal translocation of long arms of chromosome 9 and 22.[15]This translocation results in BCR/ABL fusion gene, which is translated in p210 BCR/ABL oncoprotein in most of the cases of CML. The basic biology of progression of pediatric CML to BP is still unknown, however it is considered similar to that in adults. Philadelphia (Ph1) chromosome has the inherent tyrosine kinase activity which along with BCR-ABL1 fusion gene induces granulocytic as well as blast proliferation in leukemic stem cells.[7, 12] BCR-ABL1 suppresses c-Jun, a monopoiesis-promoting transcription factor in both CML neutrophils and blasts. Thus, BCR-ABL1 fusion gene is also detected in mature neutrophils. Mature eosinophils and basophils also posses BCR-ABL1 fusion gene which causes them to proliferate.[12] As this blast crisis phase is considered mostly fatal, the main aim of treatment in CML is to hault the further progression of chronic phase which is done by in the BCR-ABL tyrosine kinase inhibitor (TKI). But still the nature of the disease is difficult to predict as 20-30% of patients develop TKI resistance due to BCR-ABL1 kinase domain mutations.[16] As in our case even studies have reported that around 15% of chronic phase patient have imatinib resistance at 18 months of treatment.[11] The second generation (TKIs) as dasatinib and nilotinib also could achieve <50%complete cytogenetic response (CCyR) in imatinib resistant/ intolerant cases.[17] Thus, transplantation is highly considered in the treatment of CML.

This case report highlights that the CML in benign chronic phase can progress to fatal blast crisis phase as early as 18 months even with TKI therapy.BCR/ABL Ratio along with cytogenetic,karyotyping and TKI sensitivity is mandatory to identify the progression of the disease and every patient needs to be counselled about HSCT disclosing the risk benefit ratio of the procedure.

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