CASE SERIES

THE RESPONSIVENESS OF CHILDHOOD/ADOLESCENT CHRONIC MYELOID LEUKAEMIA PATIENTS OF PAKISTANI ORIGIN TO TYROSINE KINASE INHIBITOR

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Chronic myelogenous leukaemia is a disease in which bone marrow produces too many white blood cells. It is more common in middle age and its incidence is rare in children. Imatinib is the standard first-line treatment in chronic myeloid leukaemia. It improved the prognosis with lesser side effects. Our point of interest is to highlight its role in the paediatric age group. we present case series of a patient with chronic myeloid leukaemia responsive to imatinib. Because of the rare incidence of chronic myeloid leukaemia in this age room limited studies to explore the role of treatment modalities in the paeds group. Our case series highlights imatinib's effectiveness in treatment and improving the prognosis of the disease in this age group.

Keywords: CML; Tyrosine kinase inhibitor

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INTRODUCTION

Chronic myelogenous leukaemia is rare in the first 20 years of life comprising only 2–3 percent of leukaemias in children.[1] It is a myeloproliferative malignancy that occurs as a result of a reciprocal chromosomal translocation between chromosomes 9 and 22 resulting in the evolution of a new oncogene BCR/ABL gene.[2] CML can present in three phases chronic, accelerated and blast phase but the common presentation the in the majority of patients is in the chronic phase.[3] CML in children and adolescents presents with features like increased white blood cell count, pallor, bleeding and splenomegaly.[4] Evolution of tyrosine kinase inhibitors phenomenally changed anticancer therapy and unlocked new treatment options and strategies.[5] Imatinib mesylate is currently ideal for first-line therapy with a standard dose of 400 mg/day for the chronic phase without causing side effects in the majority of patients.[6] It induces cell death and inhibits proliferation in BCR/ABL expressing cells through competitive blockage of ATP binding to BCR/ABL tyrosine kinase. The resistance rate is estimated at 4 percent per year.[7]

CASE 1

The patient 16 years old male Pakistan native presented with anorexia, fever, bone and joint pain and easy fat inability for 6 months. On examination, he was febrile and in pallor. Abdominal examination revealed hepato-splenomegaly. The patient had palpable cervical and inguinal lymph nodes. The respiratory, cardiovascular and musculoskeletal examination was unremarkable.

Initialcompletebloodcountresultshowedsignificantriseinwbcandplateletcount.WBCcount 102.44 (normal: 4–11 $*10^9$/L) haemoglobin 9.9 (normal: 12–16 g/dl) platelet count 550 (150–400 $*10^9$/L). Chest x-ray and echocardiography was normal. Peripheral smear report was suggestive of chronic myeloid leukaemia, revealing myelocyte 34 percent, metamyelocyte 5 percent and lymphocyte 7 percent. Uric acid was 9 mg/dl (normal: 3.5mg/dl to 7.5mg/dl) LDH989U/L (normal:140to280U/L). Serum electrolytes, renal function tests, liver function test and routine urine examination was normal.

Cytogenetic studies were done for the detection of Philadelphia chromosomes.20 cells were counted; all cells were positive for Philadelphia chromosome.

The patient was started on tab glavic 100 mg 2 tablets BD. To check the treatment response of the patient to imatinib FISH assay of the patient was repeated which was negative for BCL-ABL translocation. The patient has good adherence to treatment with proper follow-up. His recent cell counts were WBC 4.68 $*10^9$, platelet 83000 and Haemoglobin 12.1.

CASE 2

17-year-old male Pakistan native presented with fever and abdominal pain in the left hypochondrium for the last 5 months. On examination, the patient was pallor, tachypneic and short of breath.

Abdominal examination showed hepatomegaly and tenderness which was more at the right side of the abdomen. There was gross lymphadenopathy of the cervical, axillary and inguinal lymph nodes. The cardiovascular and musculoskeletal system was unremarkable. Initial CBC was done WBC count was 92.7 $*10^3$u/L (normal 4–11 $*10^3$u/L, haemoglobin was 7.4 g/d (normal 11.5 to16.5) and platelet count 492 (normal 150–400 $*10^3$u/L. Uric acid was 10.5 mg/dl (normal 3.5–7.2 mg/dl) and LDH was 1006 (normal: 140–280). Serum electrolytes, RFTS, LFTS, and routine urine examination was normal.

On peripheral smear blast cells 12 percent, promyelocyte 2 percent, myeloyte10 percent and metamyelocyte 12 perent. Furthermore, bone marrow aspiration revealed neutrophils 20%, Myelocyte 45%, Metamyelocyte 05%, blast cells 55% (blast crises), basophils 2%. Patient was admitted to provide supportive care and was started on imatinib 100 mgBD. The patient expired after 30 days due to blast crises and septicaemia.

CASE 3

A 18-years old male Pakistan native presented with fever, weight loss, joint pain, insomnia and abdominal pain for 8 months. The patient was pallor. On abdominal examination there was splenomegaly. The patient has palpable cervical and inguinal lymph nodes. Initial WBC count was $500*10^9$ (normal: 4 –11 $*10^9$), haemoglobin 6.2 and platelet count 76000. The liver function test, renal function test and serum electrolytes were normal. Chest x-ray and echocardiography was normal. Peripheral smear showed myelocyte 38% metamyelocyte 02% and blast 5%. 30 percent blast cells were present on bone marrow aspiration. BCR- ABL translocation was detected in 96 percent of the 500 nuclei counted on FISHassay.

Cytogenetics studies were done for the detection of the Philadelphia chromosome. 20 cells were counted cells were positive for the Philadelphia chromosome.

The patient was started initially with hydroxyurea and folic acid for 2 weeks and showed marked improvement in cell count with WBC $7.3*10^9$ and haemoglobin in the normal range. Imatinib was started with a dose of 200 mg BD and was continued for 2 years. After 2 years CBC showed a spikein WBC count of 18000. Treatment was changed to nilotinib 400 mg BD with regular follow-up. FISH assay was repeated that showed no BCLABL translocation in 200 nuclei scored. Currently, the patient's WBC count is normal with good follow-up.

CASE 4

A 14-year-old Pakistan native healthy and alert presented with easy fatigability, weight loss and fever for 6 months. On examination, the patient was vitally stable. On general physical examination, the patient was pallor and there was tenderness on the sternum. Abdominal examination showed splenomegaly with the size of 8 cm. Respiratory, Cardiovascular and Musculo skeletal examination was non-significant. Complete blood count revealed increased white blood cells of $122.5*10^3$/microL, Haemoglobin 9.8 g/dl and platelets $161*10^3$/microL, ESR 65 mm/hour, reticulocyte count 0.5%. Liver function tests and renal function tests were normal. Serum electrolytes, urine routine examination and Creative protein was normal.

Chest x-ray and electro-echocardiography was normal. Peripheral blood smear findings are neutrophil 56%, myelocyte was 35%, metamyelocyte was 1%, lymphocyte 3% monocytes 1%, eosinophil 1%, and blast 1%. Bone marrow is suggestive of CML in the chronic phase with increased cellularity, depressed erythropoiesis, hyperplastic and left shift myelopoiesis, increased megakaryocytes, and blast cells less than 5%. FISH assay was done for confirmation of BCL- ABL which came out positive for atypical BCR-ABL translocation. 84% of cells were positive for Philadelphia chromosomes. The patient was started on hydroxyl urea 50 mg BD after 20 days the patient has shifted to imatinib 400 mg QID after the detection of 9: 22 translocations. At the 13th day of treatment, the patient presented to the emergency department with extreme pallor, weakness and easy fatigability. WBC count was $91.17*10^9$/L, HB 10.9 and platelet was 178 $*10^9$. Repeated bone marrow was suggestive of blast crises of more than 90%. Immuno phenotyping showed CD13, CD33, CD117 MPO positive for the myeloid blast. Considering a case CML transferred to AML. He was given D3A10 for 9 days. Imatinib has changed to nilotinib 150 mg BD. Post B3A10 bone marrow examination had 85% blast considering resistant disease. FLA-DAumo chemotherapy was given for 4 days. Post FLA-DAumo bone marrow examination showed 13% blast. After 2ndFLA-DAumo chemotherapy showed a 1% blast with BCL-ABL 1 by FISH. Chemotherapy was complicated with febrile neutropenia and was managed accordingly. he was planning for a haplo bone marrow transplant with his father however his bone marrow examination before the bone marrow transplant revealed 14 % blast with aberrant expression of CD 33 by flow cytometry.

While flowcytometry by immune phenotyping showed blast with aberrant expression CD 33, positive for CD 34, HLA- DR, CD 10, CD 19, sytoCD 79a and Tdt, weak positive for CD 45 and CD117.His PCR for BCR-ABL was positive at a detection limit 33.35%. to eradicate ALL blasts, he received chemotherapy as per UKALL 2011 regimen B. Post ALL induction bone marrow examination was in morphological remission with 3–4% blast. While immune pheno typing was positive for MRD. FISH for BCR ABL gene fusion was negative. Regimen C Consolidation per UKALL2011 protocol along with

Nilotinib he developed hemiplegia. CSF was clear and MRI showed sub-acute infarct. His post-consolidation showed lymphoid blast 6%. The patient was started on 4th-generation TKIAscinminib. Side effects of treatment was reported in the form of febrile neutropenia and refractory disease.

Due to the refractory nature of the disease, the disease was considered as highly resistant. No further chemotherapy and BMT will be performed.

The patient was started on hydroxyurea and imatinib with proper follow-up.

CONCLUSION

Imatinib is the first gold-standard treatment for CML. In CML, it stops BCR-ABL protein from its role in the oncogenic pathway. In our case, series 2 patients are in the leukemic-free phase since the start of treatment. All patients showed good adherence to treatment with fewer side effects and more tolerability. One patient was presented in severe blast crises and was started on imatinib not improved and expired after 30 days. Tyrosine kinase inhibitor has a role in improving disease-free interval in our patients. Patients are currently on the treatment of tyrosine kinase inhibitors with regular follow-up.

There is significant variability in response attained with tyrosine kinase inhibitors in patients with chronic myeloid leukaemia. This variability in response could be due to adherence to treatment and the phase of chronic myeloid leukaemia. Two patients presented with CML in the chronic phase responded well to tyrosine kinase inhibitor and went into remission phase while the patient in blast crises was unresponsive.

In previous studies, patients treated with tyrosine kinase inhibitors had disease-free survival and the overall survival rate was 93.8% and 94.5% respectively.[8] Data on CML and response to TKIs throughout Asia, especially West Asia, are limited.[1] A Study on the same ethnicity comprising 101 individuals, including children and adolescents, was recruited. As a first-line TKI, Imatinib was given to 80.19 percent of patients whereas Nilotinib was administered to 19.8 percent. 88.1% attained CHR at the end of the third month. After the first year, 60.8% of patients had a molecular response (MR3). One (1%) shifted from chronic to blast phase. In 13.8% of cases, second-line TKIs were initiated owing to a lack of response.[9]

In our case reports, 50% were responsive to tyrosine kinase inhibitors while 50% were non-responsive.

Limitations

In our study, only four patients of Pakistani ethnicity were studied and a few of them are still under observation. Therefore, more studies are required to carry out on a larger scale to determine the responsiveness of this particular class of drug for childhood /adolescent chronic Myeloid Leukaemia patients.

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