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Case Report

A rare case of imatinib mesylate induced acute kidney injury

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ABSTRACT

Imatinib is a revolutionary targeted molecule strikingly successful in chronic phase of chronic myeloid leukemia and higher doses are beneficial in the accelerated phase of the disease. It's known adverse effects include abdominal pain, vomiting, fluid retention, periorbital edema, pleural effusion, myalgia, liver damage and congestive heart failure. Renal damage due to this drug has not been well reported. In this case, the patient developed acute kidney injury as evidenced by raised creatinine level after two months of administration of imatinib mesylate. At 4th visit, the levels of urea and creatinine were significantly above the upper normal limit. The patient was kept under supervision of his renal status and at the starting of 5th visit decision was made to change the drug from imatinib to nilotinib. Currently the patient is tolerating nilotinib well. Causality assessment using WHO scale revealed imatinib to have possibly caused this rare adverse reaction.

Keywords: Chronic myeloid leukemia, Imatinib, Renal failure, Creatinine

INTRODUCTION

Imatinib mesylate, a specific inhibitor of a number of tyrosine kinase enzymes including BCR-ABL has revolutionized treatment of chronic myeloid leukemia (CML) and is now the first line therapy which allows most patients to have a good quality of life when compared to the former chemotherapeutic drugs.

It is generally well tolerated. Its adverse effects include abdominal pain, vomiting, fluid retention, periorbital edema, pleural effusion, myalgia, liver damage and congestive heart failure.[1] Acute renal failure represents an infrequent side effect of imatinib, only few such cases have been reported till date.[2]

CASE REPORT

CLB, a 50 year old man presented to the Out Patient Department of Medicine of V. S. S Medical College, Burla, on 2nd May 2015, with complaints of pain and distension of abdomen, swelling of both lower limbs, constipation and malaise. The patient was normotensive, non-diabetic and euthyroid. There was no past history of tuberculosis, respiratory disease, cardiac disease, dyslipidemia or renal impairment. His personal history revealed that he smoked (10 bidis/day) and occasionally chewed betel leaf. He was not on any medication at home.

His baseline investigations revealed Hb-7 gm/dl, WBC-1.8 lacs/cumm, DLC-N68 L5 B22 E2 M0, blast cells-18%, myeloid: erythroid ratio-60:1, platelet count-2.4 lacs/cumm, serum creatinine-0.9 mg/ dl. Abdominal examination revealed hepatomegaly with massive, tender splenomegaly extending to suprapubic region. Bone marrow examination revealed hypercellular marrow with suppressed erythropoiesis and markedly accelerated granulopoiesis with all stages of maturation of myeloid series seen. Fluorescent in situ hybridization (FISH) revealed Philadelphia chromosome (t 9;22).

A diagnosis of chronic myeloid leukemia in accelerated phase was made and the patient was referred to Department of Radiotherapy, V. S. S. Medical College, Burla in May, 2015.

Patient was immediately started on imatinib mesylate 400 mg once daily orally. Whole blood transfusion was given and supportive therapy with esomeprazole 40 mg, cyanocobalamin 1000 mcg, multi vitamin, gabapentin 300 mg all were given once daily.

Table 1: Records of hematological parameters (on imatinib therapy).

Blood parameters	Visit 1 2/5/2015	Visit 2 13/6/2015	Visit 3 17/7/2015	Visit 4 22/8/2015
Hb (gm %)	7*	7*	8*	7*
WBC (/cumm)	180000*	65000*	38000*	8600
Blast cells in peripheral smear	18%*	10%*	8%*	5%*
Platelet count (/cumm)	2.4 lakh	2 lakh	1.8 lakh	1.5 lakh
RBS (mg %)	87	95	97	89
Urea (mg/dl)	27	36	35	39*
Creatinine (mg/dl)	0.9	1.24*	1.38*	2.4*

*= indicates abnormal levels.

Table 2: Records of hematological parameters (on nilotinib therapy).

Blood Parameters	Visit 5 10/9/2015	Visit 6 12/10/2015	Visit 7 15/11/2015	Visit 8 18/12/2015
Hb (gm %)	7.4*	8*	8*	8.5*
WBC (/cumm)	8000	7500	7200	7000
Blast cells in peripheral smear	5 %*	4 %*	2 %*	2 %*
Platelet count (/cumm)	1.4 lakh	1.5 lakh	1.8 lakh	2 lakh
RBS (mg %)	87	95	97	89
Urea (mg/dl)	40 *	36 *	32 *	20
Creatinine (mg/dl)	2.4 *	1.9 *	1.2 *	0.9

*= indicates significant reversal of abnormalities.

One month after starting of treatment, the edema subsided and the WBC count started reducing as revealed in Table 1. Patient was improving symptomatically and progression of CML from accelerated to blast crisis was halted. The patient was tolerating imatinib well, except that his creatinine level was raised (2.4 mg/dl) shown in Table 1. He was advised to come for monthly check up for follow up investigations. His urea and creatinine levels continued to rise at 4th visit (39 mg/dl and 2.4 mg/dl). He was referred to Nephrologist who advised him tablet sodium bicarbonate 500 mg once daily.

The patient was kept under supervision of his renal status and at the starting of 5th visit decision was made to change the drug from imatinib to nilotinib 300 mg twice a day. Slowly urea and creatinine levels started to return towards normal limits and by the end of 8th visit the levels came down to normal (20 mg/dl and 0.9 mg/dl) as shown in Table 2. But patient was still kept under supervision for his renal status because nilotinib also belongs to same group. Currently the patient is tolerating nilotinib well.

Informed consent was taken from the patient and records of his hematological parameters over a period of eight visits (from May, 2015 to December, 2015) are depicted in Table 1 and 2.

Causality assessment using WHO scale revealed imatinib to have possibly caused this rare adverse reaction.

DISCUSSION

Here is a case of chronic myeloid leukemia in accelerated phase showing significant improvement with tablet imatinib, but developing raised urea and creatinine levels indicating renal impairment, a rare event. Tong et al reported renal dysfunction during treatment with imatinib in 12% of patients with normal renal function at base line.[2] Few case reports have indicated that acute tubular necrosis (ATN) is the cause and tubular vacuolization was observed in proximal and distal tubules.[3]

The molecular mechanisms by which imatinib induces ATN are not yet understood. Imatinib targets the platelet derived growth factor receptor (PDGFR) and c-kit expressed in kidney. Proximal tubule expression of PDGFR has been reported.[4] In patients with ATN, proliferation and regeneration of proximal tubular cells depends upon PDGFR activation.[4] Therefore, imatinib

blockade of the PDGF pathway might promote ATN, especially in case of pre-existing renal failure.

Literature review revealed daily imatinib doses up to 600 or 800 mg were well tolerated by patients with mild and moderate renal dysfunction, respectively, despite their having increased imatinib exposure.[5] It may be prudent to reduce the initial dose of imatinib given to patients with severe renal dysfunction until more experience is gained in this subset of patients.

The renal injury was possibly caused by imatinib which reversed on substituting it with nilotinib. However it may be prudent to closely monitor patients on tyrosine kinase inhibitors for acute kidney injury.

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