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Imatinib induced Acute Kidney Injury: a rare Case Report

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ABSTRACT
Imatinib was the first signal transduction inhibitor (STI), used in a clinical setting. It prevents a Bcr-Abl protein from exerting its role in the oncogenic pathway in CML.In the literature it was shown that long term follow up of cases who were initially given IM suggests that approximately 60 percent will remain on IM at five years.Acute and chronic kidney injury has been rarely reported in cases that were treated with prolonged period IM for CML.In this case, the patient developed acute kidney injury as evidenced by raised creatinine level after 7 yrs of administration.Even though patient had a history of Hypertension, renal injury was suspected due to IM because serum creatinine levels were reduced on discontinuation of the drug (Imatinib). Casuality assessment was done using WHO scale and it showed that the ADR was probably caused by the drug ImtinibMesylate 400mg.The ADR was managed by Dechallenging the drug ImatinibMesylate 400mg and further treated the condition CML-CP with alternate drug Nilotinib 300mg.

Key words: Acute Kidney Injury, Imatinib, CML: Chronic Myeloid Leukemia

I. INTRODUCTION

Chronic Myeloid Leukaemia (CML) results from the neoplastic transformation of a primitive hemopoietic stem cell.[1] CML I characterized by the presence of an abnormally short chromosome 22 (Ph chromosome) resulting from a reciprocal translocation involving the long arms of chromosomes 9 and 22[2,3]. The Ph chromosome links the Bcr of chromosome 22 with the Abl proto oncogene of chromosome 9. The normal Abl gene product is a tightly regulated tyrosine kinase involved in cell division and apoptosis. The Bcr-Abl fusion gene product is a constitutely active tyrosine, the presence of which appears sufficient to induce leukemia.[4,5,6]

Imatinib was the first signal transduction inhibitor (STI), used in a clinical setting. It prevents a Bcr-Abl protein from exerting its role in the oncogenic pathway in CML. It directly inhibits the constitutive tyrosine kinase activity, which results in the modification of the function of various genes involvedin the control of the cell cycle, cell adhesion, cytoskeleton organization and finally in the apoptic death of Ph (+) cells.[7]

Imatinib associated with toxicity, though most of the adverse effects attributed occurs within the first 2yrs of starting therapy and some reverse with continued treatment at the same dose. Short term reported toxicities include >10% superficial edema, muscle cramps, nausea, musculoskeletal pain, diarrhea, abdominal pain, joint pain.1-10% pancytopenia, febrile neutropenia, Liver function tests abnormality, flushing. <1.0% pleural effusion, syncope, angioedema. Longterm toxicities; cardio toxicities, secondary malignancy, myositis, multiple sclerosis, renal failure, dermatitis, pancreatitis, hypophophatemia, gynecomastia, hypogammaglobulinemia, opportunistic infections, hepatotoxicities, pulmonary toxicities, skin hyper/hypopigmentation, cerebral edema.[8] One of the rare toxic effects of Imatinib include renal failure which contributes for <1% and here is the case report of a patient showing this rare toxic effect of the Imatinib.

II. CASE REPORT

A 66yrs old female patient presented to the casuality, department of medicine of VIMS ballari with complains of chest pain since 1 hour which was pricking type, radiating to back, associated with sweating. No H/O fever, cough.

On examination vitals were BP; 110/70mmHg, PR; 97%, RR; 16cpm and Systemic examinations were normal.

But, ECG showed ST elevation in 11-V4 and ST depression in II, III, Avf and 2D ECHO showed IHD, RWMA at rest (Anterior segment) Moderate LV dysfunction.

The past history included that patient had a known case of Hypertension on Tab. Amlodipine 5mg and CML-CP on Tab. ImatinibMesylate 500mg since 7 years.

The patient was diagnosed as Myocardial Infarction and treatment was given accordingly and the therapy includes Tab. Aspirin, Tab. Atorvastatin, Tab. Clopidogrel, Inj. Streptokinase, Inj. Heparin, Inj. Pantoprazole, Tab. Metoprolol and Tab. Imatinib was continued for CML-CP.

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Investigations

Table 1: Reports of hematological parameters (on Imatinib therapy)

Parameters	Day 1	Day 2	Day3	Day 4	Day 5	Day 6
Hemoglobin (gm%)	11.2	10.0	-	-	9.7	-
WBC(/cmm)	14000	16700	-	-	6700	-
Platelet(/cmm)	3.9lakh	3.18lakh	-	-	3.63lakh	-
RBS(mg/dl)	120	124	-	-	94	-
Blood Urea(mg/dl)	30	44	38	2.2	30	20
Sr. Creatinine(mg/dl)	2.0	1.4	1.7	44	2.0	1.4
Sodium(mEq/L)	136	139	130	132	139	133
Potassium(mEq/L)	4.6	4.3	4.5	5.1	4.2	4.9
Chloride(mEq/L)	102	108	104	103	102	104

WBC: White blood cells, RBS: Random blood sugar

The patient investigations showed normal Complete blood count, liver function tests, Random blood sugar but abnormality in renal profile that is elevation in serum creatinine levels.

Based on the objective evidence of ECG the patient was diagnosed with Myocardial Infarction and patient was treated was treated for the condition with Tab. Aspirin 75 mg, Tab. Atorvastatin 40 mg, Tab. Clopidogrel 75 mg, Inj. Streptokinase 1.5mu in 100ml NS, Inj. Heparin 5000IU, Tab. Isosorbidedinitrate 5 mg, Tab. Metoprolol 12.5 mg and Tab. ImatinibMesylate 400mg was continued for CML-CP.

On routine investigations, elevated serum creatinine levelswas noticed. And the cause for this was suspected because of Imatinibmesylate. So the drug was kept on hold and the gradual improvement in serum creatinine levels are expressed in table.1

And in order to treat CML-CP the patient was prescribed Nilotinib 300mg twice a day and asked to visit after 1 week and it seemed that the patient tolerated well and in similar way patient was asked to visit for 3 more weeks and on investigation patient showed no abnormality in her investigations stating that the patient tolerated well with Nilotinib 300 mg.

ADR Assessment and Management

Casuality assessment was done using WHO scale and it showed that the ADR was probably caused by the drug ImtinibMesylate 400mg.

The ADR was managed by Dechallenging the drug ImatinibMesylate 400mg and further treated the condition CML-CP with alternate drug Nilotinib 300mg.

III. DISCUSSION

Imatinib was the first signal transduction inhibitor (STI), used in a clinical setting. It prevents a Bcr-Abl protein from exerting its role in the oncogenic pathway in CML.[7] In the literature it was shown that long term follow up of cases who were initially given IM suggests that approximately 60 percent will remain on IM at five years.[9] Similarly our patient were under IM treatment for 7 years without encountering disease relapse or intolerancein a reversible fashion. IM treatment can be the reason of serum creatinine elevation by inhibiting tubular secretion of creatinine.[10] Tubular cells are susceptible to the toxic effects of drugs, as they have a role in concentrating and reabsorbing the glomerular filtrate, what exposes them to high levels of circulating toxins [11]. In the case of imatinib, the toxic effect may be related to platelet-derived growth factor receptor (PDGFR) inhibition [12]. . Acute and chronic kidney injury has been rarely reported in cases that were treated with prolonged period IM for CML [13,14,15]. In the literature the mean reduction in creatinine clearance was estimated as 2.77 mL/ min/1.73 m2 per year [13]. Even though patient had a history of Hypertension, renal injury was suspected due to IM because serum creatinine levels were reduced on discontinuation of the drug. The raised serum creatinine levels were reduced on discontinuation of the IM. To conclude, IM treatment may result in several reversible side effects such as raised serum creatinine level and it was manageable if patients were managed carefully.

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