Life threatening hepatotoxicity induced by Nilotinib.

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Abstract

Adverse events remain an obstacle to follow successful responding treatment. Solutions and manuscripts for monitoring drugs are essential, especially when it's about a dangerous untoward occurrence. We report the case of 57 year-old woman with chronic myeloid leukemia who developed a rare life threatening hepatotoxicity (grade 4) secondary to Nilotinib® and how we ruled this. A monitoring of the disease as well as the treatment is mandatory.

Keywords: Leukemia, Mitoses, Nilotinib, Enzyme.

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Introduction

Chronic myeloid leukemia (CML) is a common bone marrow disorder and it accounts for approximately 15% of newly diagnosed cases of leukemia in adults. Tyrosine Kinase Inhibitor (TKI)have transformed the treatment of CML and have improved the overall survival and the response rate. Since its approval in 2007, Nilotinib® has emerged as a second generation bcr-abl tyrosine kinase inhibitor with antileukemic activity remarkably effective and reasonably safe medication for the treatment of CML. We report the case of a patient with CML who developed life threatening liver toxicity secondary to Nilotinib

Case Presentation

A 57 year- old woman with no previous history particularly no liver disease, no alcohol consumption, no drug use, was diagnosed with CML on October 2017 for enormous spleen at 20 cm from the costal debord, leucocytosis 190000/µl with myelemia confirmed by the karyotype showing the presence of (9,22) translocation on all examined mitoses. Molecular studies by RT-PCR revealed the characteristic transcribed bcr-abl type b3a2 and she was diagnosed on chronic phase with Sokal=1, 5.

By December 2017, she started her treatment based on Imatinib 400 mg per day. At six months of treatment, she failed the cytogenetic and molecular response (persistence of the translocation over all studied mitoses and bcr-abl transcribed was at 25%).

A switch to a second generation of TKI was required; on September 2018, she started Nilotinib at fixed standard dose of 400mg×2/day. At that time no abnormality was in her liver, pancreatic or cardiac lab tests.

A molecular response was optimal at 6 month of treatment (bcr-abl=0, 5%) with complete cytogenetic response. The decision was to continue the same treatment (Figure 1).

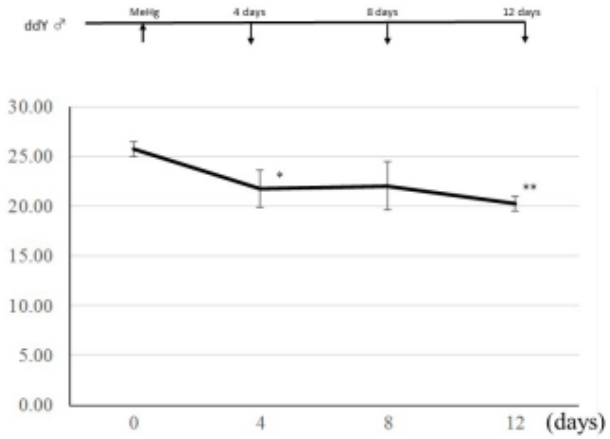

***Figure 1**. Serum transaminase and total bilirubin levels before and after nilotini treatment.*

On June 2019 (10 months of treatment with 2nd TKI), she developed a jaundice and weakness, she consults on emergency where the physical exam objectives a slight jaundice, GCS at 15, no organomegaly and the rest of examination was unremarkable.

Her laboratory tests reveal an acute severe hepatic injury with AST=32 folds, ALT=22 folds, Prothrombine=56% with cholestasis however abdominal echography was normal and viral serology were negatives. Immunologic finding was negative too (anti nuclear antibody (ANA), anti mitochondria antibody and anti liver kidney microsome type 1 antibody (ALKM1A)). An aggravation of her renal function with preserved dieresis overcame quickly.

Pharmacological investigation had incriminated the Nilotinib, the only treatment used with a score C2S2I2B3.

Nilotinib was stopped and the evolution was marked by the improvement of clinical symptoms and fall in the level of liver enzymes', decrease of mixed hyperbilirubin and normalization of creatinemia. And the patient was discharged.

At 3 months treatment free, there is normalization to strict normal of her laboratory tests despite molecular relapse bcr-abl=16%. From December 2019 she had started Dasatinib.

Molecular response at six months after was bcr-abl=0,042% and the liver laboratory tests were normal.

Discussion

Those features are a rare presentation of hepatobiliary disorders secondary to Nilotinib

Elevated hepatic enzyme's (grade 3 or 4) are seen in approximately 10-15% of patients but rarely progress to hepatitis. Why it seems uncommon? Hepatotoxicity caused by other TKI is well documented, but the frequency of Nilotinib® hepatotoxicity is rare.

In fact, Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), potentially increasing the concentration of drugs eliminated by theses enzymes. In particular, bilirubin is glucurnidated by UGT1A1, but Nilotinib inhibits bilirubin metabolism via UGT1A1, thereby increasing bilirubin level is the most common hepatic disorder.

Elevation in transaminase level of more than 5 folds the upper limit was reported in 4-9% of seminal clinical trials, and minor elevations were scary observed in up to 15% of patients.

Regard to the liver toxicity, Nilotinib effect appears so divergent. Although, we repot the case of transaminase superior to 10 folds with hepatic failure (Prothrombine inferior to 60%) and there is a similar case published on February 2019 (even the authors reported a moderately elevated transaminase and alkaline phosphatase at the start of Nilotinib Nilotinib looks like the molecule to protect liver tissue; there has been a recent interest regarding the potential efficacy of Nilotinib in the treatment of the most common forms of injury and fibrosis in the liver.

An Egyptian research article published on September 2013, details different mechanism of Nilotinib interference with Acetaminophen hepatotoxicity (abolition of induced liver injury and necro inflammation, counteracted depletion of hepatic glutathione and inhibition of its related enzymes at the dose of 25 mg/Kg, suppressed induced oxidative/ nitrosative stress cascade and neutrophil accumulation in the liver, prevent induced bcl2, cyclin D1 and c-Kit protein expressions in the liver, reduced induced mortality at the dose of 25mg/Kg). The latter exceed to the theoretical therapeutic dose which is equivalent for an adult of 80 Kg to 10mg/Kg so far the toxic threshold.

Even more, Nilotinib at a dose of 60 mg/day was the treatment of choice after a liver failure Imatinib induced and treated by liver transplant. How we had managed this case? There was no biopsy finding to confirm the type of the hepatic lesion neither a genotyping study to define the patient's metabolic profile. We obtained an excellent evolution on discontinuation of Nilotinib with normalization to strict normal at 3 months off treatment despite molecular relapse bcr-abl=16%. We opt for the use of Dasatinib from December 2019 on the purpose to obtain a therapeutic response (resistance to 1st TKI) and avoid a contact with the incriminated molecule in the liver injury. Molecular response at six months of Dasatinib was bcr-abl=0.042% and the liver lab tests were normal.

The etiology wasn't obvious, an immunologic mechanism could be in on the basis of the gender and the age and it's the second case occurring in a young woman although standard immunologic findings were negatives.

Better management; consist of a Therapeutic Drug Monitoring (TDM). Nakahara et al from Japan reported a successful dose Nilotinib adjustment after hepatic dysfunction grade 3.

Careful watch of liver function tests and TDM of TKI are the important tools for CML treatment. Pharmacokinetic parameters confer an objective gadget to supervise, ensure safety and efficacy of Nilotinib

Nilotinib Cmin (the predicted morning steady-state Nilotinib concentration) was associated with the occurrence of all grade elevation in lipase and total bilirubin. Even more, response to treatment and time to relapse could be predicted by the level of Cmin.

Conclusion

Many experimental evidences plead in favor of Nilotinib liver's protective effect but here we report a rare dangerous case of liver toxicity due to Nilotinib A monitoring of the disease as well as of the treatment is mandatory. Now available pharmacokinetic studies allow a better follow up.

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