Late Occurrence of Hyperbilirubinemia and Renal Dysfunction During Nilotinib Treatment for an Elderly Chronic Myeloid Leukemia: A Case Report

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Case report

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Abstract

**Background:** Compared with the first-generation tyrosine kinase inhibitor (TKI), Nilotinib exhibited potent inhibition for BCR-ABL kinase activity, approved of the first-line and second-line TKI treatment of CML patients. Nilotinib was generally well tolerated with mild hematologic and non-hematologic adverse events. Hyperbilirubinemia, the most common non-hematologic adverse events, was confirmed presented mostly with grade I-II, rarely with grade III-IV in several large-scale clinical trails and real-world treatment.

**Case presentation:** we report a rare case of elderly CML with severe bilirubin and creatinine elevation after receiving Nilotinib as second-line treatment for 2 years. After TKI suspension, hepatic and renal function improved quickly, but degree IV bone marrow suppression persisted for rather a long time. Monosomy 7 clone was detected at the point when renal dysfunction occurred, which indicated disease progression to accelerated phase. When Imatinib and Dasatinib were administrated alternately, a large area of acute cerebral infarction occurred unexpectedly after blood cell count recovered. So far, Imatinib treatment was continued, the patient is still stable state at the 6 months follow up.

**Conclusions:** The report alerted clinicians to observe the incidence of adverse events during long-term TKIs therapy. Also, clinicians might consider the occurrence of monosomy clone when faced with poor efficacy or intolerance.

Background

Chronic myeloid leukemia (CML), a myeloproliferative disorder, is accompanied by the production of BCR-ABL1 oncogene deriving from the Philadelphia chromosome (t(9;22)(q34;q11.2)). With the world-wide marketing of first- and second-generation tyrosine kinase inhibitors (TKIs), the 10-year survival rate of CML patients had significantly improved (2). However, the safety of long-term TKI administration has attracted much attention due to the impact of adverse events (AEs) on organ function, adherence, quality of life and even treatment outcomes. The result of a phase 3 randomized, open-label, multicenter ENESTnd trial (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients) showed the elevation of total bilirubin, aspartate aminotransferase, alanine aminotransferase was the most common AEs (3), which is comparable in real world. Nevertheless, high grade (III-IV) hyperbilirubinemia has been rarely reported, and usually got improved when nilotinib treatment continued.

Previous studies have reported that CML patients suffered chronic renal injury in long-term imatinib therapy, which could be reversed when patients switching to nilotinib therapy from imatinib (4–6). In this report, we describe a patient with CML, first treated with imatinib, then switched to nilotinib due to resistance. She developed severe jaundice and renal impairment simultaneously after two years nilotinib treatment. -7 abnormality was found when we performed karyotype analyze for her. Report about the association between TKIs, renal dysfunction and elevated bilirubin levels is reviewed and the postulated mechanisms are discussed.

Case Presentation

A 72-year-old female patient sought medical care in January 2017 with chief complaint of upper left abdominal pain, nausea in Jiangsu Province Hospital. Complete blood count analysis showed extremely high white blood cell (WBC) count 352.74×10⁹/L (neutrophils 80.7%, eosinophils 2.6%, basophils 0%), Hemoglobin 72g/L, and platelet (PLT) count 409×10⁹/L. The serum biochemical tests revealed normal hepatic and renal function. Abdominal ultrasonography displayed significant megalosplenia (187*64mm). Typical CML morphology manifestations and classic t(9;22)(q34;q11) chromosome were discovered. BCR-ABL gene was presented in 97% of interphase bone marrow cells via fluorescence in situ hybridization analysis. P190 mRNA transcripts level was 13%. Based on these, the patient was diagnosed of typical Ph positive CML chronic phase (Sokal score 0.88 intermediate risk, EUTS 2.0929 intermediate risk). The patient was initially administrated with Imatinib (400mg qd) from April 2018. Complete hematologic remission was achieved in the first month. At month 3, Ph⁺ bone marrow cells were 100%, indicating a failure signal of suboptimal response. Considering the patient’s individual request and comorbidity, Imatinib was continued. At month 6, BCR-ABL level was 47.8%, which forced treatment switch. Nilotinib 400mg twice a day was administrated as second line regimen since January 2018. However, the patient still failed to achieve satisfactory efficacy. Dasatinib is not applicable due to medical history of pulmonary hypertension of 40mmHg. The BCR-ABL quantification gradually fell to 0.87% at 2 years follow-up.

In March 2020 (26 months after switching), the patient developed gradually fatigue, poor appetite and turned yellowish skin and sclera. Pancytopenia was detected with WBC of 3.19×10⁹/L, hemoglobin of 58g/l and PLT of 63×10⁹/L, meeting grade IV suppression criteria. Also, serum test showed grade IV hyperbilirubinemia (total bilirubin 131.9μmol/L, direct bilirubin 95.7μmol/L) and renal insufficiency (blood urea nitrogen 17.97 mmol/L, creatinine 244.6 μmol/L). Nilotinib was suspended immediately, and drugs protecting hepatic and renal function were given. Viral and autoimmune hepatitis were negative, and abdominal CT revealed no space-occupying lesions. Twenty days later, organ function improved, but suppression persisted. Karotype analysis displayed the emergence of -7 clone (46,XX,t(9;22)(q34;q11.2)[3]/ 45,XX,-7[6]/ 46,XX[1]), indicating progression to accelerated phase. Imatinib 400 mg and Dasatinib 100 mg were alternatively administrated from 24 days after Nilotinib suspension. One week later, hematopoiesis function recovered with platelet count increasing to 195×10⁹/L. Eight days after, the patient complained of intermittent limb swelling and developed a loss of consciousness. CT and MRI showed acute large-scale cerebral infarction (Fig. 1). TKI was suspected again and anticoagulant therapy was administrated. Regarding higher incidence of arterial vascular events in Dasatinib than Imatinib (7), the patient resumed Imatinib 400mg. Process of the patient’s diagnosis and treatment is summarized in Table 1.
Table 1

Process of the patient's diagnosis and treatment

| Date     | Point-in-time | WBC    | Hb      | Plt    | ALT   | AST   | LDH   | TBil  | Ccr (eGFR ml/min) | Karyotype                                      | P190  | ABL mutation | Treatm       |
|----------|---------------|--------|---------|--------|-------|-------|-------|-------|------------------|-----------------------------------------------|-------|--------------|--------------|
| 2017/1   |               | 352.74 | 72      | 409    | 12    | 30.7  | 1171  | 6.2   | 76.7 (67)        | 46,XX,t(9;22)(q34;q11)                         | 13%   |              | hydrox       |
| 2017/4   |               | 9.72   | 82      | 37     |       |       |       |       |                  |                                               |       |              | Imatinib     |
| 2017/5   |               | 3.48   | 80      | 227    |       |       |       |       |                  |                                               |       |              |              |
| 2017/7   | Imatinib 3m   | 4.7    | 93      | 94     | 12.5  | 28.5  | 309   | 11    | 73.9 (70.08)     | 46,XX,t(9;22)(q34;q11)                         | 7%    |              |              |
| 2017/10  | Imatinib 6m   | 3.53   | 96      | 100    | 8.5   | 27.5  | 243   | 9.1   | 78.6(65.05)       |                                               | 10.40%| negative     |              |
| 2017/11  |               | 3.53   | 96      | 100    | 8.5   | 27.5  | 243   | 9.1   | 78.6(65.05)       |                                               | 13.90%| negative     |              |
| 2018/1   |               | 4.22   | 91      | 110    | 11.8  | 18.6  | 225   | 23.3  | 64.2 (82.5)       |                                               | 18.10%|              | Nilotini bid |
| 2018/3   | Nilotinib 3m  | 5.42   | 97      | 126    | 18.9  | 20.8  | 209   | 15.6  | 65.5(80.52)       |                                               | 23.30%|              |              |
| 2018/6   | Nilotinib 6m  | 5.3    | 94      | 138    | 14.4  | 17.2  | 178   | 17.8  | 69(75.61)         |                                               | 10.30%|              |              |
| 2018/9   |               | 6.68   | 94      | 150    | 20.2  | 23    | 165   | 21.2  | 61.6(86.72)       |                                               | 19.20%|              |              |
| 2018/10  |               | 3.44   | 96      | 100    | 8.5   | 27.5  | 243   | 9.1   | 78.6(65.05)       |                                               | 10.20%|              |              |
| 2018/4   |               | 4.22   | 91      | 110    | 11.8  | 18.6  | 225   | 23.3  | 64.2 (82.5)       |                                               | 7.70% |              |              |
| 2019/6   |               | 4.22   | 91      | 110    | 11.8  | 18.6  | 225   | 23.3  | 64.2 (82.5)       |                                               | 2.50% | negative     |              |
| 2019/12  |               | 35     | 35      | 177    | 29.6  | 59.3  | 90.17 |       | 0.87%            |                                               |       |              |              |
| 2020/3/20|               | 3.19   | 58      | 63     | 62.2  | 51.3  | 131.9 |       | 6.50%            |                                               |       |              |              |
| 2020/3/30|               | 2      | 61      | 20     | 24.5  | 24.8  | 183   | 35.8  | 219 (18.45)       |                                               | negative| Nilotini Suspen |              |
| 2020/4/10|               | 5.84   | 87      | 36     |       |       |       |       | 6.50%            |                                               |       |              | Imatinig qod an 100mg |
| 2020/4/17|               | 3.87   | 82      | 195    | 40.7  | 36.5  | 184   | 26.8  | 86(57.13)         |                                               |       |              |              |
| 2020/4/18|               | 2.38   | 69      | 165    |       |       |       |       | 71 (72.02)        |                                               |       |              | Imatinib     |
| 2020/7/16|               | 4.01   | 67      | 100    | 65    | 56    | 182   | 9.69  | 63.5(82.43)       |                                               |       |              |              |

**Discussion And Conclusions**

TKIs had turned to the first line regimen in the past decades for CML-CP patients. Nilotinib, second-generation TKI, is able to block BCR-ABL kinase activity with a 25-fold higher intensity than Imatinib, which has been approved for not only Imatinib-resistant or intolerant CML (8), but also the first line treatment for newly diagnosed CML. A phase III study showed that 12 month complete cytogenetic response rate was significantly higher in the Nilotinib group (43% for Nilotinib 400 mg twice a day vs. 22% for the Imatinib 400 mg once a day, \( P < 0.001 \)) (3). In this case, the patient initially chose Imatinib as the first line treatment, but BCR-ABL quantification was > 10% after 6 months, indicating treatment failure and then switched to Nilotinib. However, the patient still responded poor to Nilotinib though no BCR-ABL kinase mutation was found. One year later, BCR-ABL level remained 7.7%. Camgoz et al (9) found up-regulated of anti-apoptotic genes GCS, SK-1 and MRP1 genes and down-regulated of pro-apoptotic genes Bax and CerS1 in Nilotinib resistant CML cell lines. Therefore, ABL mutation independent resistance is probably the underlying mechanisms. Vinhas (10) suggested that patients who did not obtain MMR within 1 year had a higher probability of disease progression. Similarly, the patient had an abnormality with 7 chromosome deletion two years after adjustment, indicating accelerated phase according to ELN guidelines (11). Usually, monosomy 7 presents in myelodysplastic syndromes(MDS) or acute myeloid leukemia(AML) cells, associated with very poor prognosis. There is no long-term follow-up data for CML with monosomy 7 about the possibility of progressing to MDS or AML. Therefore, whether patient need further treatments or just close follow-up will be optimal strategy remains uncertain.

In this case, the patient developed rare grade IV hyperbilirubinemia after long-term treatment with Nilotinib, accompanied by acute renal impairment. Bilirubin elevation (mostly mild to moderate) generally occurred within 2 months from Nilotinib commencement(3), mainly present with unconjugated form, related to the uracil diphosphate glucuronyl transferase gene, the only gene encoding specific enzymes related to bilirubin glycolaldehyde acidification in liver (12). Among all TKIs, Nilotinib has the strongest inhibiting ability. On the contrary, combined bilirubin increased, generally caused by hepatobiliary obstruction. No medical history of cholelithiasis and no space-occupying were found. Nilotinib and its metabolites are excreted through hepatic biliary tract system, which
could probably explain the bile duct damage. In addition, the minimal concentration (C0 values) of Nilotinib was confirmed closely associated with clinical efficacy or toxicity. Patients with higher C0 values were considered to have significant higher frequency of sever hyperbilirubinemia occurrence (13, 14). TKIs-induced acute renal failure has rarely been reported. Yilmaz et al (6) found 19 cases (4%) suffered acute kidney injury (AKI) and the incidence was higher in Imatinib group than Nilotinib (P= 0.014). Multivariate analysis also confirmed that Imatinib is an independent risk factor. The elderly patient in our center did not experience AKI during the first year of Imatinib treatment but developed AKI with estimated glomerular filtration rate of 16.14ml/min two years after Nilotinib administration. In 2013, Jin (15) reported Nilotinib-related AKI, which was caused by tumor lysis syndrome (TLS). TLS is characterized by abnormal metabolism and usually occurred at the initial anti-tumor treatment. In this case, the occurrence of AKI was quite late, with no manifestations of metabolic abnormalities, no manifestations of high tumor burden. Therefore, it is speculated that renal dysfunction was multifactorial. Platelet-derived growth factor receptors (PDGFRs), involved in the formation of renal tubules was closely associated with TKI-related nephrotoxicity (16, 17). In rat ischemic injury model, PDGFRs messenger RNA expression was found enhanced. Inhibition of PDGFR β-chain/PDGFR axis by PDGFR-b selective agents may aggravate renal ischemia-perfusion injury, indicating PDGFR signaling play a role in renal tubular cell regeneration after acute tubular necrosis (18, 19). As Nilotinib has inhibitory effects on PDGFR and c-kit, it is able to interfere with the renal tubular repair mechanism mediated by PDGFR. Another potential mechanism is the effect of Nilotinib on vascular endothelium via PDGFR, participating in the regulation of vascular endothelium and surrounding cells (20). Hadzijusufovic et al (21) demonstrated that Nilotinib resulted in the development of arterial occlusive disease through exerting direct proatherogenic and antiangiogenic effects on endothelial cells. Renal biopsy in patients with elevated creatinine level after receiving Nilotinib treatment for 16 months revealed thicker vascular endothelium, resembling the damage of Nilotinib on blood vessels (22).

Dasatinib and Imatinib were administrated alternately when organ function improved, but acute cerebral infarction occurred unexpectedly. This may be due to rapid increase and aggregation of platelets. Considering the more risk of arterial vascular events in Dasatinib (7), the patient still take Imatinib for treatment so far. Tough monosomy clone was detected, no obvious blood cell count abnormality was found after 6 months. Schmidt et al (23) had proposed several models of clone evolution in CML patients, just like the situation in this case, Ph-negative clonal cytogenetic abnormalities maybe acquired before the onset of CML, and was probably masked by the predominant Ph-positive clone at the first diagnosis. When Ph-positive clones were eradicated by the TKI, Ph-negative clones persisted and maintained clonal hematopoiesis. This is probably a mechanism of the monosomy 7 clone failed to evoke MDS or AML in this case.

List Of Abbreviations
TKI: tyrosine kinase inhibitor
CML: chronic myeloid leukemia
AEs: adverse events
WBC: white blood cell
PLT: platelet
MDS: myelodysplastic syndromes
AML: acute myeloid leukemia
AKI: acute kidney injury
TLS: tumor lysis syndrome
PDGFRs: Platelet-derived growth factor receptors

Declarations
Acknowledgments
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
We obtained written informed consent from the patient's next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editors-in-Chief of this journal.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Competing interests
There were no conflicts of interest to disclosure.

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Authors' contributions

YZ and HZ designed this study, interpreted the patient data and modified the manuscript. JH and YL was a major contributor in writing the manuscript.

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Figures

Figure 1

MRI images of acute cerebral infarction. (A) T1 FLAIR (B) T2 PROPELLER (C) DWI (D) T2 FLAIR