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

Jiayu Huang

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

Yun Lian

Nanjing University of Chinese Medicine

Yu Zhu

Jiangsu Province Hospital and Nanjing Medical University First Affiliated Hospital

huihui zhao (✉ zh53030497@163.com)

Nanjing University of Chinese Medicine <https://orcid.org/0000-0002-1768-3835>

Case report

Keywords: chronic myeloid leukemia, nilotinib, hyperbilirubinemia, acute renal injury, late stage

Posted Date: April 16th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-410186/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

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 trials 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))(1). 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 $352.74 \times 10^9/L$ (neutrophils 80.7%, eosinophils 2.6%, basophils 0%), Hemoglobin 72g/l, and platelet (PLT) count $409 \times 10^9/L$. 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 $3.19 \times 10^9/L$, hemoglobin of 58g/l and PLT of $63 \times 10^9/L$, meeting grade IV suppression criteria. Also, serum test showed grade IV hyperbilirubinemia (total bilirubin 131.9umol/L, direct bilirubin 95.7umol/L) and renal insufficiency (blood urea nitrogen 17.97 mmol/L, creatinine 244.6 umol/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 $195 \times 10^9/L$. Eight days after, the patient complained of intermittent limb twitching and developed a loss of consciousness. CT and MRI showed acute large-scale cerebral infarction (Fig. 1). TKI was suspended 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) [5]	13%		hydrox
2017/4		9.72	82	37									Imatini
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) [6]	7%		
2017/10	Imatinib 6m										47.80%		
2017/11		3.53	96	100	8.5	27.5	243	9.1	78.6(65.05)		10.40%	negative	
2017/12											13.90%	negative	
2018/1		4.22	91	110	11.8	18.6	225	23.3	64.2 (82.5)		18.10%		Nilotinib
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											10.20%		
2019/4											7.70%		
2019/6										46,XX,t(9;22)(q34;q11) [4]/46,XX[6]	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	244.6(16.14)		6.50%		
2020/3/30		2	61	20	24.5	24.8	183	35.8	219(18.45)	46,XX,t(9;22)(q34;q11.2) [3]/45,XX,-7[6]/46,XX[1]		negative	Nilotini Susper
2020/4/10		5.84	87	36									Imatini 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)				Imatini
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 severe 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- β 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 PDGF-R 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). Hadzijušević 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 administered 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 took Imatinib for treatment so far. Though monosomy 7 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 may be 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.

Funding

None.

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.

Acknowledgements

Not applicable.

References

1. Marcolino MS, Boersma E, Clementino NCD, Macedo AV, Marx-Neto AD, Silva M, et al. Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients. *Ann Oncol*. 2011;22(9):2073-9.
2. Kantarjian H, O'Brien S, Jabbour E, Garcia-Manero G, Quintas-Cardama A, Shan J, et al. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience. *Blood*. 2012;119(9):1981-7.
3. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2251-9.
4. Hino A, Yoshida H, Tada Y, Koike M, Minami R, Masaie H, et al. Changes from imatinib mesylate to second generation tyrosine kinase inhibitors improve renal impairment with imatinib mesylate in chronic myelogenous leukemia. *Int J Hematol*. 2016;104(5):605-11.
5. Molica M, Scalzulli E, Colafigli G, Fegatelli DA, Massaro F, Latagliata R, et al. Changes in estimated glomerular filtration rate in chronic myeloid leukemia patients treated front line with available TKIs and correlation with cardiovascular events. *Ann Hematol*. 2018;97(10):1803-8.
6. Yilmaz M, Lahoti A, O'Brien S, Noguera-Gonzalez GM, Burger J, Ferrajoli A, et al. Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *Cancer*. 2015;121(21):3894-904.
7. Medeiros BC, Possick J, Fradley M. Cardiovascular, pulmonary, and metabolic toxicities complicating tyrosine kinase inhibitor therapy in chronic myeloid leukemia: Strategies for monitoring, detecting, and managing. *Blood reviews*. 2018;32(4):289-99.
8. Dao K, Vedy D, Lopez J, Staneczek O, Buclin T, Livio F. Imatinib-induced dose-dependent interstitial lung disease successfully switched to nilotinib: a case report with concentration exposure data. *International journal of hematology*. 2013;97(2):299-300.
9. Camgoz A, Gencer EB, Ural AU, Baran Y. Mechanisms responsible for nilotinib resistance in human chronic myeloid leukemia cells and reversal of resistance. *Leukemia & lymphoma*. 2013;54(6):1279-87.
10. Vinhas R, Cordeiro M, Pedrosa P, Fernandes AR, Baptista PV. Current trends in molecular diagnostics of chronic myeloid leukemia. *Leukemia & lymphoma*. 2017;58(8):1791-804.
11. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-84.
12. Bosma PJ, Chowdhury JR, Bakker C, Gantla S, de Boer A, Oostra BA, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *The New England journal of medicine*. 1995;333(18):1171-5.
13. Giles FJ, Yin OQ, Sallans WM, le Coutre PD, Woodman RC, Ottmann OG, et al. Nilotinib population pharmacokinetics and exposure-response analysis in patients with imatinib-resistant or -intolerant chronic myeloid leukemia. *European journal of clinical pharmacology*. 2013;69(4):813-23.
14. Larson RA, Yin OQ, Hochhaus A, Saglio G, Clark RE, Nakamae H, et al. Population pharmacokinetic and exposure-response analysis of nilotinib in patients with newly diagnosed Ph+ chronic myeloid leukemia in chronic phase. *European journal of clinical pharmacology*. 2012;68(5):723-33.
15. Hua J, Iwaki Y, Inoue M, Hagihara M. Tumor lysis syndrome soon after treatment with hydroxyurea followed by nilotinib in two patients with chronic-phase chronic myelogenous leukemia. *International journal of hematology*. 2013;98(2):243-6.
16. Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *The Journal of pharmacology and experimental therapeutics*. 2000;295(1):139-45.
17. Floege J, Eitner F, Alpers CE. A new look at platelet-derived growth factor in renal disease. *Journal of the American Society of Nephrology : JASN*. 2008;19(1):12-23.
18. Nakagawa T, Sasahara M, Haneda M, Kataoka H, Nakagawa H, Yagi M, et al. Role of PDGF B-chain and PDGF receptors in rat tubular regeneration after acute injury. *The American journal of pathology*. 1999;155(5):1689-99.
19. Takikita-Suzuki M, Haneda M, Sasahara M, Owada MK, Nakagawa T, Isono M, et al. Activation of Src kinase in platelet-derived growth factor-B-dependent tubular regeneration after acute ischemic renal injury. *The American journal of pathology*. 2003;163(1):277-86.
20. Aichberger KJ, Herndlhofer S, Scherthaner GH, Schillinger M, Mitterbauer-Hohendanner G, Sillaber C, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. *American journal of hematology*. 2011;86(7):533-9.
21. Hadzijušufovic E, Albrecht-Schgoer K, Huber K, Hoermann G, Grebien F, Eisenwort G, et al. Nilotinib-induced vasculopathy: identification of vascular endothelial cells as a primary target site. *Leukemia*. 2017;31(11):2388-97.

22. Seki Y, Nagano O, Koda R, Morita S, Hasegawa G. Pathological findings suggesting vascular endothelial damage in multiple organs in chronic myelogenous leukemia patients on long-term tyrosine kinase inhibitor therapy. *International journal of hematology*. 2020;112(4):584-91.
23. Schmidt M, Rinke J, Schafer V, Schnittger S, Kohlmann A, Obstfelder E, et al. Molecular-defined clonal evolution in patients with chronic myeloid leukemia independent of the BCR-ABL status. *Leukemia*. 2014;28(12):2292-9.

Figures

Figure 1

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