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CASE REPORT

*UGT1A1*28* and **6* polymorphisms and nilotinib-induced unconjugated hyperbilirubinemia in a Japanese patient with chronic myelogenous leukemia

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Abstract Nilotinib, a second-generation tyrosine kinase inhibitor of BCR-ABL, has shown superior efficacy compared with imatinib for the treatment of chronic myelogenous leukemia (CML). Unconjugated hyperbilirubinemia has been the most frequent adverse event with laboratory abnormality observed in clinical trials of nilotinib. The homozygosity for uridine diphosphate glucuronosyltransferase (UGT) *1A1*28* polymorphism has been reported to increase the risk of nilotinib-induced unconjugated hyperbilirubinemia in Caucasians. However, the frequency of *UGT1A1*28* is low in Asians, including Japanese. On the other hand, the *UGT1A1*6* allele mutation, which is extremely rare in Caucasians, is more frequent than the *UGT1A1*28* allele in the Japanese population. Herein, we present a patient with CML who developed grade 3 unconjugated hyperbilirubinemia after being treated with nilotinib. We found that the patient was heterozygous for both *UGT1A1*28* and **6*. Our findings suggest that the compound heterozygosity for *UGT1A1*28* and **6* could be a cause of unconjugated hyperbilirubinemia during nilotinib treatment.

Keywords Nilotinib · Hyperbilirubinemia · UGT1A1 · Polymorphism

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Introduction

Randomized phase 3 trials have revealed that nilotinib and dasatinib, second-generation tyrosine kinase inhibitors (2nd TKIs) of BCR-ABL, have superior efficacy compared with imatinib for the first-line treatment of chronic myelogenous leukemia in the chronic phase (CML-CP) [1, 2]. Currently, both these 2nd TKIs are available as the first-line treatment in newly diagnosed CML-CP. Their profiles of adverse effect are characteristic. Common adverse events (AEs) of nilotinib include myelosuppression, transient unconjugated hyperbilirubinemia, and rashes. In clinical studies of the setting for frontline treatment of CML-CP with nilotinib, 7–16 % patients had grade 3 or 4 hyperbilirubinemia [3, 4].

As for the risk factor of developing nilotinib-induced hyperbilirubinemia, the uridine diphosphate glucuronosyltransferase (UGT) *1A1* promoter polymorphism has been noticed recently. UGT1A1 catalyzes glucuronidation of hepatic bilirubin in humans. A $(TA)_7$ repeat polymorphism (termed the **28* mutation) in a TATA element in the promoter region, in place of the more common $(TA)_6$ repeat, reduces UGT1A1 expression and causes the benign elevation of unconjugated bilirubin. The homozygosity for this *UGT1A1*28* mutation was reportedly associated with an elevated risk of nilotinib-induced hyperbilirubinemia in Caucasians [5]. However, the distribution of *UGT1A1*28* differs greatly between Caucasians and Japanese, namely, the frequency of *UGT1A1*28* is high in Caucasians, whereas it is low in Asians, including Japanese [6, 7]. On the other hand, another low-activity allele 211G > A (G71R) in exon 1 (termed the **6* mutation) was frequently found in an Asian population [8].

Herein, we present a patient with CML-CP who developed grade 3 unconjugated hyperbilirubinemia after being

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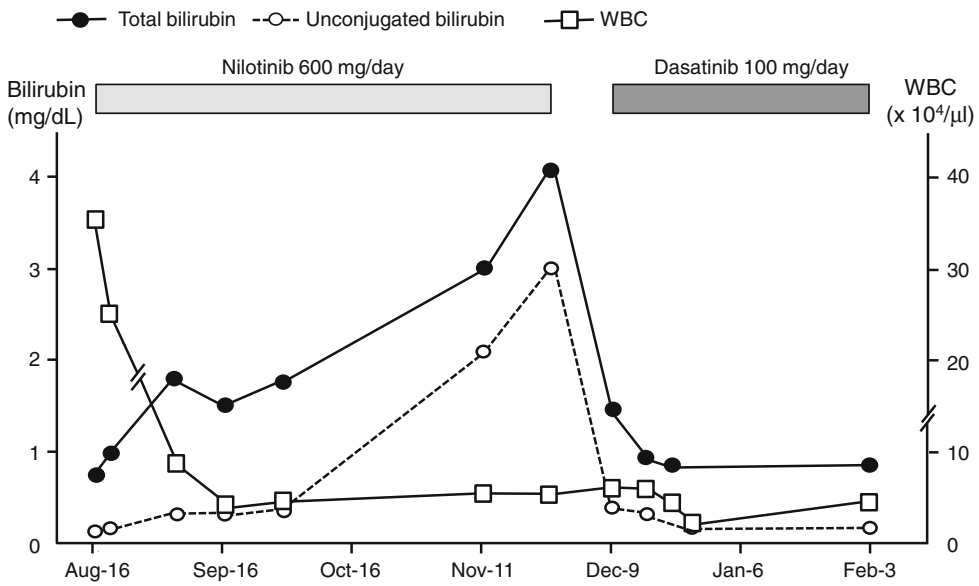

Fig. 1 Clinical course of the patient. *WBW* white blood cells

treated with nilotinib. She was not homozygous for *UGT1A1*28* but heterozygous for both *UGT1A1*28* and **6*. This is the first case that suggests that the compound heterozygosity for *UGT1A1*28* and **6* increases susceptibility to nilotinib-induced unconjugated hyperbilirubinemia.

Case report

In August 2011, a 26-year-old Japanese woman was diagnosed with CML-CP. She was started on nilotinib 300 mg twice daily (Fig. 1). Two days later, she suffered from headache, which spontaneously improved. She achieved complete hematological remission within 4 weeks. Her serum total bilirubin started to elevate during the same period, then gradually increased. Fourteen weeks later, her serum total bilirubin concentration reached 4.1 mg/dL, of which unconjugated bilirubin was 3.0 mg/dL. Other laboratory data including liver function tests were within normal ranges. We suspected a nilotinib-induced hyperbilirubinemia, and stopped nilotinib treatment. Two weeks after stopping administration of nilotinib, her total bilirubin concentration returned to normal. Then the administration of dasatinib (100 mg/day) was started. She tolerated dasatinib well without any significant AE. She achieved complete cytogenetic remission after 7 months of treatment with nilotinib and dasatinib.

We performed *UGT1A1* genotyping in our patient with written informed consent using the Invader®UGT1A1 Assay Kit (Sekisui Medical, Co., Ltd., Tokyo, Japan) according to the manufacturer's instructions. We found that she was a heterozygote for two polymorphisms, *UGT1A1*28* and **6*.

Discussion

UGT1A1 is a key enzyme in bilirubin conjugation and, in the absence of hemolysis, defects in this enzyme can cause an isolated unconjugated hyperbilirubinemia, such as Gilbert's syndrome (GS) or Crigler–Najjar syndrome. GS is characterized by mild hyperbilirubinemia, normal values in standard hepatic biochemical tests, and normal hepatic histology other than a modest increase in lipofuscin pigment in some patients. The *UGT1A1*28* polymorphism, found in the promoter area of *UGT1A1*, is the most frequent cause of GS in Caucasians. It was Singer et al. [5] who reported that nilotinib-induced hyperbilirubinemia may be associated with *UGT1A1*28* polymorphism. Individuals with the *UGT1A1*28* homozygous genotype were found to be at elevated risk of nilotinib-induced hyperbilirubinemia, with the observed relative risk varying between 4.5 and 18.0. The allele mutation *UGT1A1*28* occurs at frequencies up to 40 % in the Caucasian population and is seen in the Japanese population at lower rates (9–13 %). On the other hand, the *UGT1A1*6* allele, which is extremely rare in Caucasians, is more frequent than the *UGT1A1*28* allele in Japanese people [8–10]. Taking account of the frequency of *UGT1A1* polymorphisms in the Japanese population, we might have to consider the influence of *UGT1A1*6* polymorphism on nilotinib-induced unconjugated hyperbilirubinemia. Actually, our patient with nilotinib-induced unconjugated hyperbilirubinemia was not homozygous for *UGT1A1*28* but heterozygous for both *UGT1A1*28* and **6*.

Accumulating evidence about the effects of *UGT1A1* polymorphism on irinotecan helps support our hypothesis that *UGT1A1*6* is associated with nilotinib-induced unconjugated hyperbilirubinemia. Irinotecan, an anticancer

agent that inhibits topoisomerase I, is widely used in the treatment of colorectal, gastric, and lung cancers. However, adverse drug reactions such as severe diarrhea and neutropenia limit the dose of this drug. Irinotecan is metabolized by carboxylesterase to form an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which, in turn, is subsequently conjugated by UGT1A1 to yield an inactive form, SN-38 glucuronide (SN-38G). It has been demonstrated that genetic polymorphisms of *UGT1A1* are associated with the occurrence of AEs in irinotecan chemotherapy. In Caucasians, *UGT1A1*28* has been noted as a major mutant allele which causes AEs of irinotecan [11–14]; however, *UGT1A1*6* is significantly associated with severe neutropenia in Japanese patients who received irinotecan therapy [10, 15, 16].

The possible involvement of *UGA1A1*6* in nilotinib-induced unconjugated hyperbilirubinemia might be also suggested by a report by Kim et al. [17], which presented a Korean patient with nilotinib-induced unconjugated hyperbilirubinemia who was heterozygous for both *UGT1A1*60* and **6*.

The mechanism by which nilotinib and the *UGT1A1* genotype interact to cause an increased rate of hyperbilirubinemia is not fully defined. Preclinical studies revealed that nilotinib was not glucuronidated by UGT1A1; however, nilotinib inhibited UGT1A1 activity itself (unpublished data) [5]. Recently, Fujita et al. [18] also identified that nilotinib was a potent noncompetitive inhibitor of UGT1A1 activity. Therefore, a plausible explanation of nilotinib-induced hyperbilirubinemia in patients with a *UGT1A1* mutant allele such as *UGT1A1*28* or **6* is that the lower activity of UGT1A1 due to allele mutation would be decreased further by its inhibitor, nilotinib.

The way in which one should manage CML when nilotinib induces unconjugated hyperbilirubinemia has been uncertain. Rosti et al. [19] suggested that physicians should maintain nilotinib dose intensity without dose reductions, after presenting a successfully managed case of nilotinib-induced hyperbilirubinemia. With three interruptions of nilotinib treatment, that patient achieved a complete molecular response by a year. They concluded that hyperbilirubinemia and its management did not spoil the effectiveness of nilotinib; however, long-term follow-up would be needed to confirm the safety and efficacy of nilotinib for patients with CML complicated by hyperbilirubinemia. In addition, National Comprehensive Cancer Network (NCCN) guidelines recommend withholding nilotinib treatment when patients have grade 3 or 4 hyperbilirubinemia until the grade returns to less than 1 [20]. We also recommend to stopping nilotinib treatment until the bilirubin concentration return to normal in a safe pharmaceutical use.

Another choice may be switching TKI from nilotinib to dasatinib as presented in our report. In a clinical study for frontline treatment of CML-CP with dasatinib (the DASISION trial), the incidence of hyperbilirubinemia was only 1 %. In vitro analysis also confirmed that the inhibitory effect of dasatinib against UGT1A1 is ten times less than that of nilotinib [18]. This is a plausible reason why nilotinib but not dasatinib induced hyperbilirubinemia in the present case. The possibility that dasatinib induces its characteristic adverse effects anew should be considered; however, dasatinib was safely administrated 2 weeks after withholding nilotinib in our case.

Taken together, for individualized nilotinib treatment, genotyping of *UGT1A1*6* as well as **28* would be beneficial in Japanese patients to avoid unconjugated hyperbilirubinemia and helpful in making the choice between nilotinib and dasatinib for CML-CP treatment.

Conflict of interest We declare that there are no financial supports or relationships that may pose conflict of interest.

References

1. Saglio G, Kim DW, Issaragrisil S et al (2010) Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. New Engl J Med 362:2251–2259
2. Kantarjian H, Shah NP, Hochhaus A et al (2010) Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. New Engl J Med 362:2260–2270
3. Rosti G, Palandri F, Castagnetti F et al (2009) Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. Blood 114:4933–4938
4. Cortes JE, Jones D, O'Brien S et al (2010) Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. J Clin Oncol 28:392–397
5. Singer JB, Shou Y, Giles F et al (2007) UGT1A1 promoter polymorphism increases risk of nilotinib-induced hyperbilirubinemia. Leukemia 21:2311–2315
6. Monaghan G, Ryan M, Seddon R et al (1996) Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome. Lancet 347:578–581
7. Ando Y, Chida M, Nakayama K et al (1998) The UGT1A1*28 allele is relatively rare in a Japanese population. Pharmacogenetics 8:357–360
8. Kaniwa N, Kurose K, Jinno H et al (2005) Racial variability in haplotype frequencies of UGT1A1 and glucuronidation activity of a novel single nucleotide polymorphism 686C > T (P229L) found in an African-American. Drug Metab Dispos 33:458–465
9. Saeki M, Saito Y, Jinno H et al (2006) Haplotype structures of the UGT1A gene complex in a Japanese population. Pharmacogenomics J 6:63–75
10. Onoue M, Terada T, Kobayashi M et al (2009) UGT1A1*6 polymorphism is most predictive of severe neutropenia induced by irinotecan in Japanese cancer patients. Int J Clin Oncol 14:136–142
11. Hahn KK, Wolff JJ, Kolesar JM (2006) Pharmacogenetics and irinotecan therapy. Am J Health Syst Pharm 63:2211–2217
12. Innocenti F, Undevia SD, Iyer L et al (2004) Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 22:1382–1388
13. Ando Y, Saka H, Ando M et al (2000) Polymorphisms of UDP glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. Cancer Res 60:6921–6926
14. Ramchandani RP, Wang Y, Booth BP et al (2007) The role of SN-38 exposure, UGT1A1*28 polymorphism, and baseline

bilirubin level in predicting severe irinotecan toxicity. J Clin Pharmacol 47:78–86
15. Minami H, Sai K, Saeki M et al (2007) Irinotecan pharmacokinetics/pharmacodynamics and UGT1A genetic polymorphisms in Japanese: roles of UGT1A1*6 and *28. Pharmacogenet Genomics 17:497–504
16. Araki K, Fujita K, Ando Y et al (2006) Pharmacogenetic impact of polymorphisms in the coding region of the UGT1A1 gene on SN-38 glucuronidation in Japanese patients with cancer. Cancer Sci 97:1255–1259
17. Kim MK, Cho HS, Bae YK et al (2009) Nilotinib-induced hyperbilirubinemia: is it a negligible adverse event? Leuk Res 33:e159–e161
18. Fujita K, Sugiyama M, Akiyama Y et al (2011) The small-molecule tyrosine kinase inhibitor nilotinib is a potent noncompetitive inhibitor of the SN-38 glucuronidation by human UGT1A1. Cancer Chemother Pharmacol 67:237–241
19. Rosti G, Castagnetti F, Gugliotta G et al (2011) Physician's guide to the clinical management of adverse events on nilotinib therapy for the treatment of CML. Cancer Treat Rev 38:241–248
20. National Comprehensive Cancer Network (2012) NCCN clinical practice guidelines in oncology: chronic myelogenous leukemia. http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed 8 Apr 2012