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Venetoclax dose adjustment due to drug-drug interactions: a case report and literature review

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The primary aim of the study is to discuss the potential interactions between venetoclax and common drugs used in department of hematology and the corresponding effects on the efficacy and safety of venetoclax treatment. Here, we report an acute myeloid leukemia patient treated with venetoclax and posaconazole, and the dose of venetoclax was adjusted due to drug interactions. Clinical pharmacists actively participated in treatment of this patient to provide pharmacy care to assist clinicians to identify the venetoclax-induced liver function impairment and give timely management. The case reported here is hoped to provide reference for clinical venetoclax treatment in patients with such disease. Clinical pharmacists should actively participate in clinical treatment, actively screen potential drug interactions, strengthen cooperation and communication with doctors, provide patients with high-quality pharmaceutical services, and establish clinical pharmacists' status in the multidisciplinary treatment of tumor. ***Anti-Cancer Drugs*** **35: 70–75 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Acute myeloid leukemia (AML) is seen most commonly in the elderly with the median age at diagnosis of 68 years. It was reported that patients aged 60 years or older and without undergoing stem-cell transplantation had a poor prognosis, and the disease-free survival rate was only 2.4% at 10 years after diagnosis [1]. Venetoclax is a potent, selective, and oral inhibitor for Bcl-2 [2,3]. It is currently approved for treatment of AML in China while chronic lymphocytic leukemia (CLL) in the entire world. Moreover, it is also available in clinical treatment of multiple hematologic diseases such as multiple myeloma and myelodysplastic syndrome [4,5]. However, Venetoclax is metabolized mainly by CYP3A enzymes and serves as a P-gp substrate, which make it largely affected by interactions with drugs, resulting in wide-range adverse drug reactions (ADRs) and increase in disease severity. Existing studies point out that the frequent ADRs associated with Venetoclax administration mainly include hematologic abnormalities, infection, tumor lysis syndrome (TLS), hypokalemia, liver function impairment, and hyperglycemia, etc [6]. Here, we report an AML case treated with Venetoclax in our hospital. The relationship between liver function impairment and Venetoclax was analyzed from the perspective of drug interaction so as to provide reference for further medication in this population.

Case report and treatment

A 47-year-old female (weight: 53 kg; height: 155 cm) visited our hospital in March 2021 due to a high fever, shivering and muscle soreness. Routine blood test demonstrated the white blood cells (WBC) count of 1.02×10^9/L↓, erythrocyte count of 2.78×10^{12}/L↓, hemoglobin (Hb) of 98 g/L↓, absolute neutrophil count of 0.16×10^9/L↓, and platelet (PLT) count of 126×10^9/L. Bone marrow smear showed decreased myelodysplasia with an increase in promyelocytic cells (40%) and a decrease in erythroid hyperplasia. Neither megakaryocytes nor bone marrow particles were found, and PLT were visible in scattered piles. AML was diagnosed, and the patient underwent hematopoietic stem-cell transplantation in Shanghai First People's Hospital in August 2021.

On 19 May 2022, the patient was admitted to our hospital for a fever and diarrhea. Intestinal fungal infection was diagnosed and managed by Posaconazole (200 mg tid po). In the meantime, bone marrow examination revealed up-regulated expression of EVI1 gene, suggesting disease progression. On June 5, 2022, Azacitidine (100 mg qd) and Venetoclax (200 mg qd) were started. On 3 June 2022, the liver function test prior to chemotherapy demonstrated the alanine aminotransferase (ALT) of 46 U/L and the aspartate aminotransferase (AST) of 28 U/L. On 9 June 2022, the ALT and AST increased to 193 U/L↑ and 147 U/L↑, respectively. The clinical pharmacist assessed it as drug-induced liver injury, and the effect by drug interaction could not be excluded. Considering that the antifungal treatment had been sustained for

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Table 1 **Naranjo's ADR evaluation scale**

Questions	Pertinent score			Patient score
	Yes	No	Unknown	
Are there previous conclusion reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was administrated?	+2	−1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administrated?	+1	0	0	+1
Did the adverse reaction reappear when the drug was readministrated?	+2	−1	0	−1
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	0
Did the reaction reappear when a placebo was given?	−1	+1	0	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	+1
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total score				+5

Casual associations between drug(s) and ADRs are classified as definite (≥9), probable (5–8), possible (1–4), and doubtful (≤0) based on the total score.

more than 20 days, Posaconazole was recommended to be temporarily discontinued. In addition, Venetoclax was also recommended to be removed due to the risk of exacerbation of the liver injury, and symptomatic treatment using magnesium isoglycyrrhizinate and reduced glutathione was performed. On June 13, 2022, liver function test results improved with the ALT of 49 U/L and AST of 51 U/L. Treatment with Azacitidine (100 mg/d) + Venetoclax (200 mg qd) + Posaconazole (200 mg tid) was scheduled. Referring to literature, the liver insufficiency of the patient might be caused by the increased Venetoclax plasma exposure resulting from drug interactions. Therefore, the dose of Venetoclax was recommended to be reduced to 100 mg qd. On June 18, 2022, liver function test revealed the ALT of 64 U/L and the AST of 59 U/L. The patient was uneventfully discharged.

On 2 August 2022, the patient was admitted for the second cycle of chemotherapy. Considering the occurrence of liver injury in the first cycle and the sustained use of Posaconazole, the dose of Venetoclax remained at 100 mg qd, as the clinical pharmacist suggested. On August 3, 2022, liver function test before administration demonstrated the ALT of 49 U/L and AST of 59 U/L. On 4 August 2022, the second cycle of chemotherapy with Azacitidine (100 mg/d) + Venetoclax (100 mg/d) was started. On 10 August 2022, liver function test revealed the ALT of 64 U/L and AST of 51 U/L. The treatment scheme was continued and proceeded uneventfully. Additionally, patients continued to receive the same treatment regimen for the following 3–5 cycles, all without liver damage.

Discussion

Correlation between venetoclax and liver function impairment

The patient had a definitive diagnosis and was treated with a simple medication regimen. After the first cycle of chemotherapy, the patient had abnormal liver function, which improved after drug withdrawal and symptomatic treatment. Liver function tests revealed neither abnormality during the 20-day period of Posaconazole administration nor recurrence during Posaconazole administration after liver function improvement. Therefore, Posaconazole could be largely excluded as the culprit of liver injury. Additionally, azacitidine could be also excluded given the invariant dose during treatment. It was noted that there was no abnormality of liver enzymes after the dose of Venetoclax administrated was reduced, and the patient scored 5 points on the Naranjo's ADR evaluation scale (Table 1) [7]. The probability that liver function impairment was related to Venetoclax administration was therefore classified as 'probable'. It could be inferred that the liver function impairment in this patient was largely caused by Venetoclax administration.

Drug-induced liver injury is any impairment of liver function due to the use of a drug. Abnormalities in liver function due to drug ingestion can range from asymptomatic elevation of liver enzymes to acute liver failure [8].

The mechanisms of drug-induced hepatotoxicity can be divided into several categories. Firstly, the direct mechanism relates to the accumulation of the drug in the body after ingestion, that is, the accumulation of the drug and its metabolites in the liver after ingestion of the drug, resulting in direct damage. It is dose-dependent and predictable [9]. The second is the specific mechanism, which is usually mainly related to individual differences and not significantly related to dose, and is therefore neither dose-dependent nor predictable [10]. This type of liver injury is usually the result of immune-mediated liver damage or direct cellular damage [11]. It often leads to hepatocellular damage by impairing protective mechanisms, such as Nrf 2 pathway mediated activation of antioxidant genes and their proteins [12]. Thus, specific mechanisms of liver injury are often accompanied by a hypersensitivity syndrome. A third mechanism is indirect liver injury by increasing the risk of metabolic syndrome, which in turn increases the risk of non-alcoholic fatty liver disease, characterized by the accumulation of triglycerides in the liver [13,14]. In this case, it is reasonable to assume that the high plasma exposure of venetoclax directly contributed to the liver damage.

Table 2 Drug interaction probability scale

Questions	Pertinent score			Patient score	Comments
	Yes	No	Unk		
1. Are there previous credible reports of this interaction in humans?	+1	−1	0	+1	At the time of the report, 1 clinical trial report [14] multiple doses of posaconazole increased mean venetoclax Cmax and AUC
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	−1	0	+1	Posaconazole can inhibit CYP3A4.
3. Is the observed interaction consistent with the known interactive properties of object drug?	+1	−1	0	+1	Venetoclax is a substrate for CYP3A4 and P-glycoprotein.
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	−1	0	+1	The time course of the change in the change of ALT and AST would be consistent with a change in its treatment and adjustment.
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (If no dechallenge, use Unknown or NA and skip Question 6)	+1	−2	0	NA	Stopped both venetoclax and posaconazole.
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	−1	0	NA	NA
7. Are there reasonable alternative causes for the event?	−1	+1	0	+1	See in the main manuscript.
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0	0	Due to TDM limitations, we were unable to monitor the blood levels of venetoclax.
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0	0	There was no other evidence of the interaction.
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased	+1	−1	0	+1	No further hepatic impairment occurred after venetoclax dose reduction in combination with posaconazole during follow-up treatment.
Total score				+6	

Highly probable: >8; probable: 5–8; possible: 2–4; doubtful: <2.

Correlation between venetoclax-associated hepatoxicity and drug-drug interactions

The patient scored 6 points on the Drug Interaction Probability Scale (Table 2) [15]. The probability that liver function impairment was related to the potential drug-drug interaction between venetoclax and posaconazole was therefore classified as 'probable'. Referring to previous literature, venetoclax is metabolized mainly by CYP3A enzymes and serves as a substrate of P-gp, while Posaconazole is an inhibitor for both CYP3A4 (strong) and P-gp. Therefore, combination of venetoclax with Posaconazole led to a significant increase in venetoclax plasma exposure due to drug interactions, thereby resulting in ADR.

Venetoclax-associated drug-drug interactions in hematology

Interaction between venetoclax and CYP3A inhibitors including posaconazole

Azole antifungal agents are indispensable in prevention of multiple invasive fungal diseases (IFD) in high-risk patients, such as the population with hematological malignancies, and also play an important role in treatment. In patients with hematological malignancies, the risk of developing IFD can be assessed by factors such as the tumor type, treatment, and the expected duration of neutrophil decrease, while azole antifungal agents are often needed for prevention and treatment of IFD [16].

Itraconazole, Posaconazole, Ketoconazole and Voriconazole are common antifungal agents used in Department of Hematology, and they are also strong inhibitors for CYP3A enzymes. Multiple studies have pointed out that concomitant use of strong inhibitors for CYP3A while Venetoclax administration during the dose-escalation phase is prohibited. After escalation, dose reduction by at least 75% is recommended if strong inhibitors for CYP3A are necessary, and the dose can be restored only 2–3 days after the inhibitors are discontinued [17,18]. In a recent study of Bhatnagar *et al.* [19], the interaction between Posaconazole and Venetoclax was studied by using a physiologically based pharmacokinetic model. The authors found that the combined use of 70 mg Venetoclax and 500 mg Posaconazole led to an increase in the Venetoclax plasma exposure, in comparison to the use of 400 mg Venetoclax alone, whereas the exposure was still within the safe range.

Some weak inhibitors for CYP3A, such as Ciprofloxacin, Fluconazole and Verapamil, also have significant drug interactions with Venetoclax. When used in combination, the dose of Venetoclax is recommended to be reduced by 50%, and the potential ADRs should be closely monitored.

In the present study, the patient had liver function impairment after the combination treatment with Venetoclax and Posaconazole, which was suspected as a result of the increased Venetoclax plasma exposure resulting from drug interactions. The dose of Venetoclax was reduced

to 100 mg qd, and the liver enzymes returned to normal without any further abnormalities. It could be seen that Venetoclax is largely affected by interactions with other drugs. Clinical pharmacists suggest that medication reconciliation before Venetoclax administration and active monitoring of potential ADRs are extremely important in clinical Venetoclax administration.

Interaction between venetoclax and P-gp substrates and inhibitors

Venetoclax is a substrate and inhibitor of P-gp and BCRP. Chiney *et al.* [20] found that the combined use of Digoxigenin (0.5 mg) and Venetoclax (100 mg) increased the mean C_{max} and $AUC_{0\text{-inf}}$ of Digoxigenin to 1.35 (90% CI:1.16–1.59) and 1.09 (90% CI: 1.00–1.20), respectively, while the T_{max} remained invariant. If necessary, Venetoclax can be used in combination with other P-gp substrates, whereas the P-gp substrates are recommended to be administrated at least 6 h prior to Venetoclax administration.

In another study [21] that evaluated the interaction between P-gp inhibitor Azithromycin and Venetoclax, the C_{max} (mean: 0.75; 90% CI: 0.6–0.86) and $AUC_{0\text{-inf}}$ (mean: 0.65; 90% CI: 0.58–0.73) of venetoclax were abnormally decreased after a combined use, whereas the T_{max} remained invariant. The result also indicates that not all P-gp inhibitors can lead to a large increase in Venetoclax plasma exposure. Similarly, a population pharmacokinetic analysis including 505 subjects demonstrated that there was no change in pharmacokinetics of venetoclax after a combination with P-gp inhibitors [22]. Actually, the instructions on Venetoclax suggests a minimum 50% decrease in Venetoclax dose when it is used in combination with P-gp inhibitors such as Azithromycin [17]. According to the studies mentioned above, Venetoclax can be administrated without dose adjustment when there is a need to use in combination with Azithromycin or other P-gp inhibitors. Clinical pharmacists suggest that active medication reconciliation (including to avoid combination or reduce dose) can increase the safety of Venetoclax administration.

Interaction between venetoclax and CYP3A inducers such as carbamazepine

Multiple CYP3A inducers, such as Carbamazepine, Phenytoin and Rifapentine, can significantly reduce the plasma exposure of Venetoclax. Agarwal *et al.* [23] performed a phase I clinical trial in healthy people to study the interaction between Venetoclax and CYP3A inducer Rifapentine. Rifapentine is a strong inducer of CYP3A and also a substrate of P-gp. In this study, the plasma exposure of Venetoclax was comparatively analyzed in people treated with Venetoclax alone and Venetoclax plus single-dose Rifapentine or Venetoclax plus multi-dose Rifapentine, in an attempt to distinguish between the chronic CYP3A-induced net effect and the P-gp inhibition effect. In comparison to Venetoclax alone, Venetoclax + single-dose Rifapentine increased the C_{max} and AUC of Venetoclax by 106% and 78%, respectively; while Venetoclax + multi-dose Rifapentine reduced the C_{max} and AUC of Venetoclax by 42% and 71%, respectively. After conversion, the authors noted that induction of CYP3A decreased the C_{max} and AUC of Venetoclax by 72% and 84%, respectively. These findings indicate that the induced metabolic effects of CYP3A play a major role in in-vivo metabolism of Venetoclax, in spite of that Venetoclax is also a substrate of P-gp. It could be seen that the combination of CYP3A inducer with Venetoclax may lead to a decrease in Venetoclax plasma exposure and then affect the effectiveness and safety of Venetoclax administration. In clinical practice, clinical pharmacists are required to be active to assist clinicians to avoid the combination treatment with potentially significant drug interactions.

Medication reconciliation during venetoclax administration

The plasma exposure of Venetoclax is largely influenced by drug interactions, while the drugs that can interact with Venetoclax are diverse. In clinical practice, medication reconciliation is recommended prior to administration in all patients scheduled for Venetoclax treatment to avoid unnecessary potential drug interactions as much as possible. In addition, close monitoring during treatment is required, and timely intervention is necessary. After discharge, patients should be follow-up regularly to avoid Venetoclax treatment failure resulting from drug interactions due to the intake of additional drugs, foods or some health products.

TLS represents the most important characteristic ADR of Venetoclax. In an early study in CLL patients, the authors noted that Venetoclax might cause TLS in CLL patients and lead to TLS-related death. Therefore, dose-escalation per week was recommended [24]. In addition, dose-escalation is also recommended currently in Venetoclax treatment for AML to avoid TLS, while the dose is increased incrementally every day [25]. Since the therapeutic window for TLS is narrow, Venetoclax should be avoided in combination with inhibitors for CYP3A4 and P-gp in the dose-escalation phase. While in the maintenance period, combination treatment should be used with caution. It is reported that combination with strong inhibitors for CYP3A4 and P-gp can increase the Venetoclax plasma concentration and exposure, resulting in increased risk of developing TLS or other adverse events. Ideally, such strong inhibitors for CYP3A4 and P-gp should be permanently or temporarily prohibited when Venetoclax is administrated to decrease potential risks. In case there is a need for combination, the target dose of Venetoclax should be reduced. For instance, in patients concomitantly

treated with azole antifungal agents, the target dose of Venetoclax should be reduced from 400 mg qd to 200 mg qd or 100 mg qd. Moreover, nephrotoxic drugs that may worsen kidney function and TLS, such as nephrotoxic antibiotics (e.g. Vancomycin) and non-steroidal anti-inflammatory drugs, should be also avoided in clinical practice [26].

In recent years, more within-county tumor patients have the opportunity to get treatment in primary hospitals, owing to the active promotion of integrated health-care service and the functional localization of county-level hospitals in hierarchical diagnosis and treatment system. Various new anti-tumor agents, especially the orally bioactive agents, have been increasingly used in tumor patients from county-level hospitals, but most of the hospitals fail to provide well-established surveillance service. In this context, timely effective medication reconciliation and close monitoring appear more meaningful, as such management can efficiently help increase the efficacy and safety of treatment in tumor patients from county-level hospitals.

Significance of monitoring venetoclax plasma concentration during treatment

The plasma exposure of Venetoclax is largely influenced by drug interactions, while the drugs that can interact with Venetoclax are diverse. Therefore, monitoring drug concentration during Venetoclax treatment has some clinical significance. Besides safety, the therapeutic efficacy of Venetoclax is also linked with the serum drug concentration. The study of Freise *et al.* [27] reported a significant association ($P < 0.01$) between Venetoclax plasma exposure and progression-free survival (PFS) in recurrent or refractory CLL patients, and it was noted that Venetoclax at 800 mg qd brought more benefit to PFS than Venetoclax at 400 mg qd. Another study of the same research team also revealed that the complete remission rate increased with increasing Venetoclax plasma exposure in this patient population [28]. Presently, research on monitoring serum Venetoclax concentration during treatment is still less. To our knowledge, there are only two methodological studies published [29,30], and no clinical intervention study is performed to prove the effect of serum drug concentration on treatment safety. Both the two existing studies reported that the steady-state trough concentration of Venetoclax during treatment in AML patients fluctuated in a range of 250–8000 ng/ml. Therefore, we believe that monitoring serum drug concentration during Venetoclax administration might be an effective approach to help achieve individualized clinical medication thus to increase safety. In hospitals where the conditions are permitted, clinical pharmacists can try to provide individualized Venetoclax medication using the TDM approach.

Summary

This study reports an AML patient who developed liver function impairment after combination treatment with Venetoclax and Posaconazole. Pharmacy care was provided by clinical pharmacists during the whole treatment process to assist clinicians in medication reconciliation. Finally, the liver function of the patient improved after the dose of Venetoclax was reduced by 50%. This study gives a hint that there are many targeted small-molecule drugs metabolized by liver microsomal enzymes, which makes drug interactions relatively frequent [31]. In AML patients, usually multiple drugs are needed to combine due to the previous comorbidities. In this context, a poor understanding of the interactions between targeted small-molecule drugs and a lack of proper management will affect the efficacy and safety of treatment in these patients, especially in hospitals where drug monitoring is not supported. Furthermore, clinical pharmacists should actively participate in treatment of these patients to find potential drug interactions, provide opinions for medication reconciliation, actively communicate with the clinicians and give timely interventions, which is conducive to rational clinical medication.

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JG and YZ finished data and case curation. WF and RZ performed the case analysis and literature review.WF wrote the first draft of the manuscript and BL finished the manuscript review and editing. All authors reviewed and approved the final version of the manuscript.

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Consent for publication: Informed consent for this publication was obtained from the patient before the submission of this case report.

Conflicts of interest

There are no conflicts of interest.

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