İstanbul Journal of Pharmacy
Istanbul J Pharm2024, 54 (3): 345–349
DOI: 10.26650/IstanbulJPharm.2024.1330470

Original Article

Drug-drug interactions with venetoclax in acute myeloid leukemia

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ABSTRACT

Background and Aims: Venetoclax is an important treatment option, especially in patients who are unfit for acute myeloid leukemia treatment. However, because venetoclax is metabolized by CYP3A4, it can lead to many drug-drug interactions (DDIs). DDIs may make a drug less effective, cause unexpected side effects, or increase the action of a particular drug. This study aims to examine venetoclax-related DDIs in this vulnerable patient population and to illuminate possible interventions for both patients and clinicians.

Methods: This observational study was performed between November 2018-December 2022 in the Department of Hematology, Erciyes University Faculty of Medicine. The study involves 60 patients and uses Lexi-interact® to determine potential DDIs (pDDIs) in all patients and uses Lexi-interact® to take into account category D and category X interactions.

Results: Forty-seven (78.4%) patients experienced drug interactions. The most common drug interactions were with azole antifungals, most commonly with posaconazole in category D (31.6%). Clarithromycin and diltiazem were found in more than 20% of patients. Carbamazepine, phenytoin and cladribine were found as contraindicated (category X) drugs.

Conclusion: The study shows that at least 78.4% of the patients treated with venetoclax were at risk of DDIs. Dose reduction of venetoclax is necessary when used with azole antifungals. Due to the extremely high occurrence of DDIs, pharmacists have a significant role in drug interaction management in the multidisciplinary team.

Keywords: Acute myeloid leukemia, Interaction, Posaconazole, Venetoclax

INTRODUCTION

Acute myeloid leukemia (AML) remains challenging in the elderly and/or unfit patients, with the long-term prognosis being generally poor (Juliusson et al., 2009). Venetoclax is a BH3 mimetic and small molecule inhibitor of the anti-apoptotic B cell-lymphoma-2 (BCL-2) (Vervloessem et al., 2017). The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine for patients over 75 years of age or who have comorbidities that preclude the use of intensive induction chemotherapy. Drug interactions become even more important in elderly patients due to the use of multiple drugs (Delafuente, 2003).

Venetoclax has many drug-drug interactions (DDIs). As stated in Venclyxto's summary of product characteristics (SmPC; AbbVie Inc, North Chicago, IL), cytochrome P-450 (CYP450) 3A4 is the primary enzyme responsible for the metabolism of venetoclax, as well as an enzyme that causes drug interactions. The SmPC states, "Caution should be exercised when using Venclyxto with inhibitors of the CYP3A4 family (such as voriconazole, posaconazole) [or the] concurrent use of venetoclax with strong CYP3A4 inducers such as carbamazepine, phenytoin" (EMA, 2002).

As a BCL-2 inhibitor, venetoclax is a substrate of the drug efflux transporter p-glycoprotein in vivo and in vitro (Agarwal, Tong, Bueno, Menon, & Salem, 2018). Pharmacists play a significant role in drug management. In such a particularly sensitive patient population, a multidisciplinary team should be involved with regard to such situations as DDIs, side effect prevention, and dose adjustment (Ma, 2014). In addition, pharmacists play an essential role in terms of the benefits and risks of treating patient and their caregivers by increasing patient participation and shared decision making (Rocque et al., 2018).

This article aims to study all potential DDIs (pDDIs) ob-

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Submitted: 24.07.2023 • **Revision Requested:** 27.10.2023 • **Last Revision Received:** 28.11.2023 • **Accepted:** 08.12.2023

served in patients treated with venetoclax. The study also emphasizes the importance of multidisciplinary work involving pharmacists.

MATERIALS AND METHODS

This retrospective study performs a systematic analysis of all aspects of patient treatment to detect potential clinically significant interactions (CSIs) and involves patients with acute myeloid leukemia (AML) using venetoclax between January 1, 2018-December 31, 2022. The study has included 60 patients with AML who were followed up in the Hematology Department of the Medical Faculty of Erciyes University. The Erciyes University Clinical Research Ethics Committee approved this study in accordance with the Declaration of Helsinki (Decision No. 2022/711). The study obtained patient information retrospectively from the patients' electronic medical records. The following data were collected: age and gender of the patient, drugs prescribed, and adverse drug reactions (ADRs). The study's clinic routinely checks the digoxin serum concentrations in patients using digoxin. This only applies to digoxin. Digoxin serum concentrations are routinely monitored in patients' electronic medical records.

The study determined the pDDIs using Lexi-interact® to classify CSIs as category D or category X. Table 1 shows the classification of drug interactions by severity (Marion, 2022). Some interventions (e.g., dose modification, close monitoring, alternative treatments) are required to minimize toxicity in order to achieve beneficial results. The benefit-to-harm ratio of using multiple drugs should be determined. In Lexi-interact®, category D interactions are interactions with proven clinical significance, while category X interactions are interactions where the risk outweighs the benefit and thus their concomitant use is contraindicated (Marion, 2022).

Table 1. *Severity of Drug Interactions*

Severity of Drug Interaction	Up to Date
Contraindicated	X = Contraindicated
Major	D = Consider therapy modification
Moderate	C = Monitor Therapy
Minor	B = No action needed
None	A = No known interaction

The study performs a descriptive analysis of the variables. Central tendency and dispersion (*SD*) measures are used for the quantitative variables. Frequency distributions have been calculated for the qualitative variables. The statistical analyses are performed using SPSS® v. 25.0.

RESULTS

This retrospective study includes 60 patients, of whom 36 (68.7%) are male. The patients' mean age is 65.50 ±16.9 years. At least one drug was able to interact with venetoclax in 47 (78.4%) patients. The number of pDDIs ranged from one to three, totaling 73 pDDIs (Table 2).

Table 2. *Distribution of Patients According to the Number of pDDIs with Venetoclax*

Number of pDDIs with venetoclax	Number of patients $N = 60$ n (%)
0	13 (21.6%)
1	25 (41.6%)
2	18 (30%)
3	4 (6.8%)

Table 3 shows the distribution of patients according to drugs that were able to interact with venetoclax. The most frequent is posaconazole (31.6%), and this interaction is able to increase venetoclax's toxicity. More than 10% of patients also had pDDIs with carbamazepine (5%) or phenytoin (1.6%), which were able to decrease venetoclax effectiveness, and concomitant use with the degree of interaction X is contraindicated. Drug interactions in category X have also been detected with cladribine.

DISCUSSION

This study is critical for patients with hematological malignancies who also receive treatment with sensitive CYP3A substrates, such as venetoclax. Venetoclax is a new drug approved for use in AML in 2018. Studies are ongoing regarding the use of venetoclax in many other diseases/conditions. Venetoclax is metabolized by CYP3A4 and requires more attention in terms of its drug interactions. As one of the consequences of DDIs in this study, as the drug serum concentration increases, the dose may need to be reduced. If the dose is not reduced, the toxicity of the drug increases as the serum concentration increases, and the drug may need to be discontinued. As a result, situations occur such as the interruption of patient treatment and discontinuation of a costly treatment. The most common side effects are hematological and gastrointestinal toxicity.

This study saw the most common interactions with azole antifungals, diltiazem, and clarithromycin. The most common drug interactions occurred with posaconazole in category D (31.6%). One of the reasons for this is that patients had been given prophylactic antifungals (Maertens et al., 2018). Azole antifungals lead to increased concentrations of venetoclax, because azole antifungal agents inhibit CYP3A4 to varying degrees. CYP3A4 is the primary enzyme responsible for metabolizing venetoclax; therefore, adding azole antifungals reduces its metabolism (Agarwal et al., 2017). The steady dose of venetoclax should be 70 mg/day when used with posaconazole in patients with AML (Bhatnagar et al., 2021). When venetoclax is used concomitantly with a strong CYP3A4 inhibitor such as voriconazole,

Table 3. *Increase or Decrease in Drug Exposure or Effect*

Drugs able to interact with venetoclax	# of patients *N* =60 *n* (%)	Increase ↑ or decrease ↓ of drug exposure	Severity of drug interaction
Posaconazole	19 (31.6)	Venetoclax ↑	D
Fluconazole	17 (28.3)	Venetoclax ↑	D
Diltiazem	7 (11.6)	Venetoclax ↑	D
Voriconazole	6 (10)	Venetoclax ↑	D
Clarithromycin	6 (10)	Venetoclax ↑	D
Cladribine	3 (5)	Immunosuppressive effect ↑	X
Digoxin	3 (5)	Digoxin ↑	D
Carbamazepine	3 (5)	Venetoclax ↓	X
Amiadarone	3 (5)	Venetoclax ↑	D
Aprepitant	2 (3.2)	Venetoclax ↑	D
Carvedilol	2 (3.2)	Venetoclax ↑	D
Phenytoin	1 (1.6)	Venetoclax ↓	X

the venetoclax dose should be reduced by 75%. A 50% dose reduction is required with a moderate CYP3A4 inhibitor such as fluconazole (Venclexta, 2019). Rausch et al. (2021) showed that the platelet healing process was prolonged despite dose reduction. In a retrospective study of AML patients treated with venetoclax and hypomethylating agents (HMAs), concomitant use of posaconazole/voriconazole plus 100 mg/day of venetoclax or 200 mg/day of isavuconazole/fluconazole plus venetoclax was compared with azole-free plus full-dose venetoclax. As a result of another study, higher febrile neutropenia, infection risk, and increased hospitalization were observed in those using azole plus venetoclax (Chiney, Menon, Bueno, Tong, & Salem, 2018). Therefore, venetoclax should be used more carefully in patients receiving azole antifungals.

Venetoclax may increase digoxin concentrations, a substrate of p-glycoprotein, with concomitant use. Avoid concomitant use of venetoclax and digoxin if possible. If combined, administer digoxin at least 6 hours before venetoclax to minimize the potential for interaction (Venclexta, 2019; Chiney et al., 2018). Digoxin toxicity is more likely to develop at digoxin serum concentrations of 1.2 ng/mL or greater. The current study found one patient with an increased digoxin serum concentration observed at 1.8 ng/mL. The dose of digoxin was reduced in this patient. Little research has been done on this, and more is needed. Because of venetoclax's narrow therapeutic range, monitoring digoxin levels should be considered in patients who receive venetoclax in combination with digoxin.

This study has found cladribine, carbamazepine, and phenytoin to interact in category X. When considering the interaction of venetoclax with cladribine, this interaction appears contraindicated. However, treatment regimens are also found in which cladribine and venetoclax have been used together. For this reason, drug interactions need to be evaluated by a specialist clinical pharmacist (Kadia et al., 2021).

Clarithromycin and diltiazem increase the level of venetoclax by inhibiting CYP3A4. Clarithromycin is a potent CYP3A4 inhibitor, while diltiazem is a moderate CYP3A4 inhibitor. When venetoclax is used concomitantly with clarithromycin, the venetoclax dose should be reduced by 75%, while the dose of venetoclax should be reduced by 50% with diltiazem (Freise, Shebley,& Salem,2017). Much attention has been paid to the interaction of venetoclax with azole antifungals. Caution should also be exercised with other drugs that increase venetoclax's serum concentration. The patients receiving clarithromycin in the current study had been switched to a different and more appropriate antibiotic.

The use of venetoclax is contraindicated in patients taking carbamazepine and phenytoin. The mechanism for this is that these drugs reduce the level of venetoclax by inducing CYP3A4 (Venclexta, 2019). The drugs carbamazepine and phenytoin were replaced with appropriate antiepileptics in the patients in this study to avoid low response rates to venetoclax. Some patients were found with double and even triple drug interactions. No study could be found on what to do in these cases.

Awareness of patients' drug interactions with hematological malignancies is crucial for pharmacotherapy. This is related to the high incidence rate for drug interactions and the importance of the consequences of these interactions. Clinical pharmacy is a branch of pharmacy that involves the provision of patient care with the use of medications to optimize patients' health outcomes and includes promoting wellness and preventing disease. The practice of clinical pharmacy embraces the philosophy of pharmaceutical care. In this case, having pharmacists be part of the healthcare team and involved in drug manage-

ment is crucial. In addition, clinical pharmacists' knowledge of prescription monitoring, detection, and management of interactions makes the clinical pharmacist the most qualified personnel for fulfilling this task. Further studies are also needed to understand the importance and magnitude of drug interactions in patients with hematological malignancies.

Meanwhile, this study has some limitations. Due to being a retrospective study, the results of drug interactions could not be monitored beyond the information in the patients' files (e.g., digoxin level). The study also could not measure venetoclax levels to see the outcomes of drug interactions.

CONCLUSION

This study suggests that at least 78.4 % of patients treated with venetoclax are at risk of DDIs. This paper also identifies the drugs with the highest rate of pDDIs (category D) with venetoclax as azole antifungals (i.e., posaconazole, fluconazole, voriconazole), clarithromycin, and diltiazem. The study also observed that a high percentage of the patients had experienced DDIs, including contraindicated (category X) drug combinations. Increased digoxin levels were found in one patient, and the dose of digoxin had been reduced in this patient. Although preventing these DDIs is difficult at times, serious situations such as increasing or decreasing the level of side effects and drug ineffectiveness may occur due to the increase in the level of venetoclax. Therefore, a strong need exists for high awareness of DDIs in order to manage patient care well. This is more important in settings such as hematology that involve cytotoxic agents. As a multidisciplinary team member that treats patients with hematological malignancies, clinical pharmacists can contribute by conducting a systematic review of treatment, identifying interactions, and making recommendations such as optimizing drug therapy and reducing drug-related problems in these patients.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee approved this study in accordance with the Declaration of Helsinki (Decision No. 2022/711).

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study: Ş.E.T., S.Ç. A.Ü.; Data Acquisition: Ş.E.T., S.Ç.; Data Analysis/Interpretation: Ş.E.T., S.Ç.; Drafting Manuscript: Ş.E.T., S.Ç.; Critical Revision of Manuscript: Ş Ş.E.T., S.Ç.; Final Approval and Accountability: Ş.E.T., S.Ç., A.Ü.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared no financial support.

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REFERENCES

Agarwal, S.K., DiNardo, C.D., Potluri, J., Dunbar, M., Kantarjian, H.M., Humerickhouse, R.A., . . . Salem, A.H. (2017). Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. *Clinical Therapeutics, 39* (2), 359-367. doi: 10.1016/j.clinthera.2017.01.003.

Agarwal, S.K., Tong, B., Bueno, O.F., Menon, R.M., & Salem A.H. (2018). Effect of azithromycin on venetoclax pharmacokinetics in healthy volunteers: implications for dosing venetoclax with p-gp inhibitors. *Advances in Therapy, 35*, 2015–2023. doi: 10.1007/s12325-018-0793-y

Bhatnagar, S., Mukherjee, D., Salem, A.H., Miles, D., Menon, R.M., & Gibbs, J.P. (2021). Dose adjustment of venetoclax when co-administered with posaconazole: clinical drug–drug interaction predictions using a PBPK approach. *Cancer Chemotherapy and Pharmacology, 87*, 465–474. doi: 10.1007/s00280-020-04179-w

Chiney, M.S., Menon, R.M., Bueno, O.F., Tong, B., & Salem, A.H. (2018). Clinical evaluation of p-glycoprotein inhibition by venetoclax: a drug interaction study with digoxin. *Xenobiotica, 48*(9), 904-910. doi: 10.1080/00498254.2017.1381779.

Delafuente, J.C. (2003). Understanding and preventing drug interactions in elderly patients. *Critical Reviews in Oncology/Hematology, 48*(2), 133-143. doi: 10.1016/j.critrevonc.2003.04.004.

European Medicines Agency EPAR Product information on venetoclax vencylxto. (2002). Erişim adresi https://www.ema.europa.eu/en/medicines/human/EPAR/venclyxto.

Freise, K.J., Shebley, M., & Salem, A.H. (2017). Quantitative prediction of the effect of CYP3A inhibitors and inducers on venetoclax pharmacokinetics using a physiologically based pharmacokinetic model. *Journal of Clinical Pharmacology, 57* (6), 796-804. doi: 10.1002/jcph.858

Juliusson, G., Antunovic, P., Derolf, A., Lehmann, S., Möllgård, L., Stockelberg, D., Tidefelt, U., . . . Höglund, M. (2009). Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish acute leukemia registry. *Blood, 113*, 4179–4187. doi: 10.1182/blood-2008-07-172007.

Kadia, T.M., Reville, P.K., Borthakur, G., Yilmaz, M., Kornblau, S., Alvarado, Y., Dinardo, C.D., . . . Kantarjian, H.M. (2021). Venetoclax plus intensive chemotherapy with cladribine, idarubicin, and cytarabine in patients with newly diagnosed acute myeloid leukaemia or high-risk myelodysplastic syndrome: a cohort from a single-centre, single-arm, phase 2 trial. *The Lancet Haematology, 8* (8), 552-561. doi: 10.1016/S2352-3026(21)00192-7.

Ma, C. (2014). Role of pharmacists in optimizing the use of anticancer drugs in the clinical setting. *Pharmacy Research and Practice, 3,* 11-24. doi: 10.2147/IPRP.S40428

Maertens, J.A., Girmenia, C., Brüggemann, R.J., Duarte, R.F., Kibbler, C.C., Ljungman, P., Racil, Z., . . . Cordonnier, C. (2018). European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. *Journal of Antimicrobial Chemotherapy, 73* (12), 3221-3230. doi:

10.1093/jac/dky286.

Marion, D.W. Diaphragmatic pacing. In: UpToDate, (2022). Erişim adresi http://www.lexi.com.

Rocque, G.B., Williams, C.P., Halilova, K.I., Borate, U., Jackson, B.E., Van Laar, E.S., Pisu, M., . . . Safford MM. (2018). Improving shared decision-making in chronic lymphocytic leukemia through multidisciplinary education. *Translational Behavioral Medicine, 8* (2), 175-182. doi: 10.1093/tbm/ibx034.

Rausch, C.R., DiNardo, C.D., Maiti, A., Jammal, N.J., Kadia, T.M., Marx, K.R., Borthakur, G., . . . Konopleva, M.Y. (2021). Duration of cytopenias with concomitant venetoclax and azole antifungals in acute myeloid leukemia. *Cancer, 127* (14), 2489-2499. doi: 10.1002/cncr.33508.

Venclexta (venetoclax) [prescribing information]. (2019). Erişim adresi https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf

Vervloessem, T., Ivanova, H., Luyten, T., Parys, JB., . . . Bultynck, G. (2017). The selective Bcl-2 inhibitor venetoclax, a BH3 mimetic, does not dysregulate intracellular Ca2+ signaling. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1864*(6), 968-976. doi: 10.1016/j.bbamcr.2016.11.024.

How cite this article

Tubay, Ş.E., Çelik, S., Ünal, A. (2024). Drug-drug interactions with venetoclax in acute myeloid leukemia. *İstanbul Journal of Pharmacy, 54*(3): 345–349. DOI: 10.26650/IstanbulJPharm.2024.1330470