Exposure toxicity of venetoclax in acute myeloid leukemia patients in the real-life setting: impact of high exposure on delayed neutropenia

Venetoclax is a selective and potent B-cell lymphoma-2 (BCL-2) inhibitor that has improved clinical outcomes in combination with a hypomethylating agent (HMA) for patients with untreated acute myeloid leukemia (AML) unfit for intensive chemotherapy.[1] Venetoclax undergoes hepatic metabolism involving CYP3A4 and is highly sensitive to drug-drug interaction with triazoles, as well as moderate-to-strong CYP3A4 inhibitors, which are indicated during induction phase in AML for prophylaxis and treatment of Aspergillus and Candida infections.[2,3] A 75%-reduction dose of venetoclax is therefore recommended in case of combination.[4] However, the level of dose reduction is less than the 6-fold expected reduction in venetoclax clearance, which can lead to venetoclax overexposure despite an adapted dose. Venetoclax therapeutic drug monitoring (TDM) was therefore applied in routine practice. As the exposure-toxicity relationship remains unclear, the main objective of this study was to assess the risk of high exposure-related neutropenia beyond the first cycle of treatment in a real-life setting.

Patients followed in the Hematology Department of Saint-Louis, Saint-Antoine and Cochin Hospitals of Public Assistance of Parisian Hospitals with TDM in routine care centrally performed in Saint Louis Hospital Pharmacology Department between January 1, 2018 and October 31, 2021 were retrospectively selected. This retrospective study was approved by the institutional review board (IRB) 00006477 of HUPNVS, Paris 7 University, AP-HP IRB (number: CER-2022-159). Patient inclusion in the pharmacokinetic (PK) analysis and the exposure-toxicity analysis is described in the *Online Supplementary Figure S1*. The exposure-response analysis was performed on the subgroup of AML patients with an evaluation of medullar blast clearance after 1 month of venetoclax (between day 20 and day 35) and with data available on toxicity during the second month of treatment. Neutropenia was the criterion selected to assess the toxicity of venetoclax. Drug-related neutropenia was defined by grade ≥3 neutropenia (i.e., <1,000 neutrophil/mm^3 according to the common terminology criteria for adverse events [CTCAE] v5.0) lasting at least 7 days beyond cycle 1 day 30 of venetoclax treatment, and/or with clinical impact of pursuit of treatment (dose reduction or delay in the second month of treatment), and unrelated to the disease (i.e., in patients with <5% of bone marrow blasts at the first assessment performed between day 20 and day 35 of venetoclax treatment).

Blood samples were collected at any time during a dosing interval at steady state. Venetoclax quantification in plasma was performed using a validated liquid chromatography coupled to mass tandem spectrometry according to ICH M10 on bioanalytical method validation. Venetoclax plasma concentrations were analyzed using population PK approach to standardize the PK parameter estimation method between patients with sparse data. Several structural models were tested (1 or 2 compartments) inter-individual and inter-occasion variability were assessed for all PK parameters. Covariates already described as influencing PK parameters were tested in our model (i.e., age, sex, combination with CYP3A inducer, CYP3A inhibitor, ATP binding cassette inhibitor or rituximab[5]). Each covariate was tested first in univariate analysis (a decrease in objective function value (ΔOFV) of at least 3.84 χ^2 test, df=1, [P<0.05] and a significant decrease in interindividual variability was used for selecting covariates). All significant covariates were added in a multivariate model, followed by backward selection. Once the final PK model validated, it was used to estimate individual PK parameters by a Bayesian approach. Then individual PK parameter were used to determine the cumulative area under the curve (AUC) taking into account actual venetoclax daily dosing during the first 28 days. A daily average of AUC (AUCavg) was used as metric for venetoclax exposure. Model development and Bayesian *post hoc* estimation were performed with NONMEM version 7.4.1 (ICON Development Solutions, Ellicott City, MD, USA), using the first-order conditional estimation with interaction estimation method.[6]

Patients' clinical and biological characteristics are presented in terms of median (range) for quantitative variables and number (%) for qualitative variables. Association between drug-related neutropenia and venetoclax exposure (AUCavg) as well as with clinical characteristics at venetoclax initiation was assessed by univariate logistic regression models. Variables displaying a significant association with drug-related neutropenia in univariate analysis (P<0.05) were candidate for multivariate analysis and a stepwise procedure based on Akaike information criteria (AIC) minimization was conducted to compute multivariate models. Venetoclax AUCavg was considered first as a continuous variable, then an event risk threshold of AUCavg was determined by a ROC curve analysis and used as binary covariate. All analyses were carried out using R software version 4.2.4 (R Core team 2013).

A total of 123 patients (corresponding to 280 samples) were eligible for the PK analysis, mainly with AML (62.6%),

chronic lymphocytic leukemia (CLL, 8.9%), multiple myeloma (MM, 8.1%), and myelodysplastic syndromes (MDS, 8.1%) as presented in *Online Supplementary Table S1*. Among the 79 patients treated for AML presented in Table 1, there was a majority of men with high-risk AML according to European LeukemiaNet (ELN) 2017 citeria.[7] Venetoclax was prescribed mostly as continuously daily dosing in combination with HMA, mostly concomitantly to a strong CYP3A inhibitor. The median daily dose of venetoclax after ramp-up reached 400 mg (interquartile range [IQR], 200-400), whereas it was decreased to 100 mg (IQR, 100-200) in case of interaction with a strong CYP3A inhibitor. Among the 51 patients with available bone marrow assessment after cycle 1, drug-related toxicity was not evaluable for 22 of them because bone marrow blasts were still ≥5% after cycle 1. Thus, 29 patients were included in the exposure-toxicity analysis.

A 1-compartment model with one-order absorption and elimination fitted the data better than a 2-compartment model (ΔOFV=59.1; P<0.001). Two covariates influencing apparent oral clearance (CL/F) were kept in the model: strong CYP3A inducer (ΔOFV=20.3; P<0.001) and strong CYP3A inhibitor (ΔOFV=124.78; P<0.001). The underlying hematological disease did not impact venetoclax PK (ΔOFV=0.539; P>0.1). The combination with a strong CYP3A inhibitor led to near to 5-fold decrease of CL/F, whereas a combination with a strong CYP inducer led to near to 3-fold increase in CL/F. Parameters values are shown in *Online Supplementary Table S2*. The correlation between predicted and observed individual concentrations illustrates the fit of the model and therefore its ability to estimate individual PK parameters (*Online Supplementary Figure S2*).

Among 29 assessable patients, 20 drug-related neutropenia

Table 1. Patient's characteristics.

Characteristic	Overall N=51	Blasts <5%* N= 29
Age in years, median (range)	72 (17-87)	72 (25-84)
Sex, N (%) M F	 33 (64.7) 18 (35.3)	 18 (62.1) 11 (37.9)
Body weight kg, median (range)	69 (40-94)	67 (43-85)
WHO PS ≥2, N (%) Unknown	14 (28.0) 1	7 (24.1) 0
Hb at baseline g/dL, median (range) Unknown, N	8.90 (6.00-15.00) 1	8.90 (6.90-13.90) 1
Leukocytes at baseline x10^9/L, median (range) Unknown, N	3 (0-84) 1	2 (0-20) 1
Neutrophil count at baseline x10^9/L, median (range)	0.70 (0.03-22.54)	0.57 (0.03-13.79)
High-risk AML at diagnosis (ELN 2017), N (%)	40 (78.4)	24 (82.8)
Refracory/relapse AML before venetoclax, N (%)	17 (33.3)	7 (24.1)
Secondary AML at diagnosis, N (%)	30 (58.8)	16 (55.2)
Regimen, N (%) Venetoclax-azacitidine Venetoclax-azacitidine-ivosidenib Venetoclax-cytarabine Venetoclax-decitabine Venetoclax-enasidenib Venetoclax-ivosidenib Venetoclax-midostaurine	 42 (82.4) 1 (2.0) 3 (5.9) 2 (3.9) 1 (2.0) 1 (2.0) 1 (2.0)	 24 (82.8) 1 (3.4) 2 (6.9) 1 (3.4) 0 (0.0) 0 (0.0) 1 (3.4)
N of monthly days of venetoclax, N (%) 8 14 21 28	 1 (2.0) 4 (7.8) 5 (9.8) 41 (80.4)	 1 (3.4) 2 (6.9) 2 (6.9) 24 (82.8)
TDM performed during first cycle, N (%)	45 (88.2)	27 (93.1)
ddi with strong CYPA inhibitor (posaconazole)**, N (%)	42 (82.4)	26 (89.7)
ddi with ABC (P-gp or BCRP) inhibitor, N (%)	44 (86.3)	25 (86.2)

*Percentage of medullar blasts after 1 month of venetoclax therapy. **One patient received also ritonavir. M: male; F: female; WHO PS: World Health Organization performance status; Hb: hemoglobin; AML: acute myeloid leukemia; ELN: European LeukemiaNet; TDM: therapeutic drug monitoring; ddi: drug-drug interaction; ABC: ATP binding cassette; P-gp: P-glycoprotein; BCRP: Breast Cancer Resistance Protein.

were observed: 18 leading to a decrease in dose intensity of venetoclax during the second cycle: as a delay of at least 7 days for venetoclax rechallenge (N=9), a decrease in number of day of venetoclax intake (N=6), a definitive venetoclax withdrawal (N=2), or a dose decrease (N=1). Two patients had grade ≥3 neutropenia lasting at least 7 days while maintaining the venetoclax dose.

Higher AUCavg was significantly correlated to drug-related neutropenia considering AUCavg above the first quartile (*P*=0.002) or above the median value (*P*=0.022) (Figure 1). Based on ROC curve analysis an AUCavg of 2.70 μg/mL day was found to be a threshold value for higher risk of drug-related neutropenia (specificity =88.9%, sensitivity =75.0%). AUCavg above this threshold was significantly associated with drug-related neutropenia (odds ratio [OR]=24.0; *P*=0.007). The secondary nature of AML was the only other covariate associated with drug-related neutropenia. The association between AUCavg above 2.70 μg/mL day remained significant even in multivariate analysis (OR=39.8; *P*=0.010) (Table 2).

In this retrospective real-life study, we described a statistically significant correlation between venetoclax exposure and drug-related neutropenia lasting beyond cycle 1 day 30 whereas the PK/PD analysis performed during the development studies failed to show any clear exposure-toxicity relationship. In our population PK model, we observed a great influence of strong CYP3A inhibitors on CL/F by factor close to five, which was slightly lower but consistent with that of previous drug-drug interaction (DDI) studies.[4] The observed coefficient on CL/F was consistent with that observed in large population PK analysis performed in a CLL population.[8] We observed higher venetoclax AUC levels than those described by Brackmann *et al.*. i.e., the range of the first quartile of AUCavg level in our study reached the range of the third quartile Brackmann *et al.*[9] The venetoclax exposure we observed was also greater than those predicted by a modeling approach in case of DDI with a strong CYP3A inhibitor, exceeding the maximum level of exposure assessed for safety.[10] In a *post hoc* analysis using data from phase I to phase III studies, Brackmann *et al.* observed no statistically significant relationship between exposure and treatment emergent grade ≥3 neutropenia but without any precision on timing of neutropenia assess-

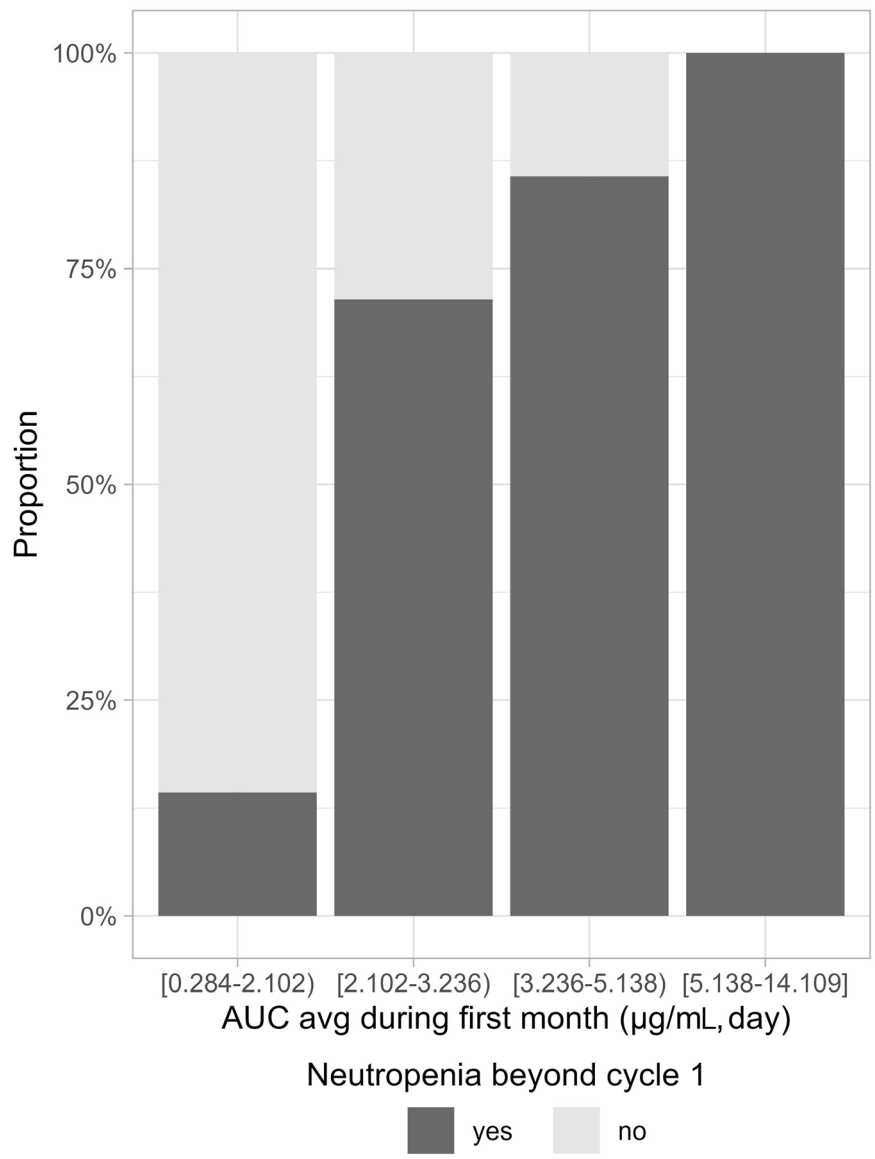

Figure 1. Incidence of drug-related neutropenia beyond cycle 1 day 30 according to daily average of area under the curve observed during the first month of treatment with venetoclax. AUCavg: average of area under the curve.

Table 2. Logistic regression exploring the correlation between daily average of area under the curve of venetoclax during the first month and the risk of clinically relevant toxicity at the beginning of the second month of treatment (N=29).

Characteristic	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Sex: F *vs.* M	0.67	0.13-3.49	0.6	-	-	-
WHO PS ≥2	3.43	0.46-70.9	0.3	-	-	-
Relapsed/refactory AML	0.50	0.08-3.16	0.4	-	-	-
Secondary AML	8.17	1.48-67.0	0.025	15.0	1.58-385	0.039
High-risk AML (ELN 2017)	0.50	0.02-4.13	0.6	-	-	-
Age >65 years	2.40	0.45-13.2	0.3	-	-	-
AUCavg >2.70 μg/mL day	24.0	3.29-507	0.007	39.8	3.78-1,472	0.010

OR: odds ratio; CI: confidence interval; F: female; M: male; WHO PS: World Health Organization performance status; AML: acute myeloid leukemia; ELN: European LeukemiaNet; AUCavg: average of area under the curve.

ment.[9] When focusing on post-remission patients included in the VIALE-A study,[11] Pratz *et al*. showed a correlation between average venetoclax concentration and any grade 4 cytopenia events.[12] Despite the retrospective nature of our study, the missing data such as the use of a granulocyte colony-stimulating factor report and the limited number of patients with complete PK and pharmacodynamics data, we observed a relation between high venetoclax exposure and toxicity which rises the question of a benefit of a shorter duration treatment. Response rates and overall survival obtained with 28-day regimen were comparable to those reached with 14-day regimen[13] or 7-day regimen.[14] Furthermore, Mirgh *et al*. observed a lower hematologic toxicity without any difference in response rate with less than 21 days of venetoclax compared to 21-28-day duration.[15]
Our study is to the best our knowledge the first exposure-toxicity study showing that a very high level of venetoclax exposure can be reached in clinical practice leading to an increased risk of drug-related neutropenia.

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LG acts as a consultant for Abbvie. All other authors have no conflicts of interest to disclose.

Contributions

Conceptualization by LG and FP. Data curation by FP, ER, LA, TH, RI, DB, LA, FR, MS, AV, EB, MM, AB, AG, JZ, LW, LD, AC, EL and LG. Formal analysis, methodology development, software development, data validation, visualization and writing of the original draft by FP, ER, LA, TH, RI, DB, LA, FR, MS, AV, EB, MM, AB, AG, JZ, LW, LD, AC, EL and LG. Resources provided by FP, ER, LA, TH, RI, DB, LA, FR, MS, AV, EB, MM, AB, AG, JZ, LW, LD, AC, EL and LG. Supervision by LG. Writing review and editing by LG.

Data-sharing statement

Data are available upon request.

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