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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Myelomonocytic/Monocytic Subtypes Are More Resistant to Venetoclax-Based Therapy in Acute Myeloid Leukemia Patients: A Monocentric, Real-Life Retrospective Study

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Background:
Venetoclax(VEN)-based regimens have seen broad adoption in newly diagnosed patients with acute myeloid leukemia (AML) who are not candidates for intensive induction chemotherapy. Nonetheless, a sizable proportion of AML patients do not respond. Finding biomarkers that can predict treatment results is crucial. FAB (French, American, British) classification system provides a well-described and clinically associated means to segregate AML patients by virtue of myeloid differentiation status. Whether FAB classification can be used as a predictor marker for VE-based therapy is controversial. In the Chinese population of patients with AML, we conducted this single center retrospective study to examine the predictive value of monocytic and myelomonocytic differentiation on the response to VEN-based treatment.
Methods:
The clinical features, treatment information, and clinical outcomes of AML patients who received at least one dose of VEN treatment at West China Hospital for more than seven days between January 1, 2019, and September 8, 2022 were retrospectively examined in this study. We classified the patients into two groups based on the FAB classification system: the primitive group (includes M0/M1/M2, abbreviated as PRI) and the myelomonocytic/monocytic group (includes M4/M5, abbreviated as M/M). AML response to VEN therapy was determined by the 2017 European Leukemia Net response criteria after one cycle of VEN treatment. The overall response rate (ORR) was defined as the combination of CR, CRi, PR. From the first day of VEN use until the patient dies or the end of follow-up, the overall survival (OS) time is calculated. Logistic regression and COX regression were used to examine the variables that influence ORR and survival. All statistical tests were two-sided, and p-values of 0.05 or lower were considered significant. All statistical analyses were performed using RStudio 4.2.2.
Results:
There were 267 patients in all, with 162 newly diagnosed (M/M n=69; PRI n=93) and 85 relapsed/refractory (M/M n=44; PRI n=41). The ORR for M/M is 63.77%, while that for PRI is 84.95% among newly diagnosed patients (p=0.018). The ORR for M/M is 40.91% and PRI is 68.29% among relapsed/refractory patients (p=0.0114, Figure1). In addition, we identified (i) FAB classification M/M subtypes, (ii) previously diagnosed MDS/MPN, (iii) IDH1/IDH2 mutations, (iv) relapsed/refractory event, (v) transfusion requirement, and (vi) TP53 mutation as significant factors predicting the response of all patients using univariate logistic regression analysis. M/M subtypes and MDS/MPN also trended toward independent predictors in the multivariate analysis. We identified (i) FAB Classification M/M subtype, (ii) adverse risk AMLs according to the 2022 ELN classification, (iii) CEBPA mutation, and (iv) TP53 mutation as significant factors predicting the risk of all patients using univariate COX regression analysis. M/M subtype and TP53 also trended toward independent predictors in the multivariate analysis (Table1). OS was significantly longer in the PRI than in the M/M(median OS: 621 days vs 266 days, hazard ratio 0.56, 95% CI: 0.39-0.80, p=0.0011). We compared the overall survival of various illness conditions; OS still was significantly longer in the PRI group than in the M/M group among newly diagnosed patients (median OS: newly diagnosed: 1124 days vs 295 days, HR: 0.47, 95% CI: 0.24-0.83, p=0.0017; refractory/relapsed: 204 days vs 266 days, HR 0.68: 95% CI: 0.45-1.97, p=0.72).
Conclusion:
Our research demonstrates that the response to VEN may differ depending on how advanced the AML is, with PRI patients being more sensitive and M/M patients being more resistant, particularly in newly diagnosed individuals. Previous research

has discovered that AML cells with Monocyte/erythroid/Megakaryocyte differentiation are less sensitive to BCL-2 inhibition in vitro, indicating that the differentiation stage of AML may affect its sensitivity to BCL-2 family inhibitors. This is likely due to an increase in MCL1 family expression and a decrease in BCL2 family expression during cell differentiation. In conclusion, M/M subtype may be able to predict VENs resistance and the worse prognosis for patients treated with VEN-based regimens.
Legends to figures
Figure 1: Differences in ORR and NR (no response) between M/M and PRI in newly diagnosed and relapsed/refractory patients
Table1: Regression analysis results

Disclosures No relevant conflicts of interest to declare.

Table 1.Univariate and multivariate analyses for response(Logistic regression) and survival(Cox Regression)

Characteristics	Response achievement		Survival	
	univariable OR (95%CI,P)	multivariablex OR (95%CI,P)	univariable HR (95%CI,P)	multivariable HR (95%CI,P)
Age(continuous variable)	1.01 (0.99-1.02, p=0.454)		1.01 (1.00-1.02, p=0.139)	
Sex(Male vs Female)	0.97 (0.56-1.65, p=0.897)		1.32 (0.92-1.89, p=0.129)	
ELN 2022 risk group				
Favorable vs Adverse	0.57 (0.30-1.07, p=0.080)	0.80 (0.30-2.16, p=0.664)	0.62 (0.40-0.96, p=0.032)	0.93 (0.56-1.55, p=0.788)
Intermediate vs Adverse	0.56 (0.21-1.48, p=0.240)	0.98 (0.28-3.48, p=0.973)	0.60 (0.32-1.13, p=0.113)	0.90 (0.44-1.81, p=0.762)
FAB Classification(Primitive vs Myelomonocytic/Monocytic)	0.31 (0.17-0.54, p<0.001)	0.30 (0.14-0.62, p=0.001)	0.56 (0.39-0.80, p=0.001)	0.65 (0.44-0.96, p=0.031)
Previously diagnosed MDS/MPN	2.28 (1.06-4.88, p=0.035)	2.90 (1.07-7.84, p=0.036)	1.37 (0.82-2.30, p=0.229)	
Extramedullary Infiltration	2.64 (0.92-7.58, p=0.070)	1.82 (0.48-6.96, p=0.379)	2.21 (1.24-3.94, p=0.007)	1.55 (0.81-2.96, p=0.187)
Transfusion requirement Hb(U)	1.05 (1.03-1.08, p<0.001)	1.02 (0.97-1.08, p=0.453)	1.03 (1.01-1.04, p<0.001)	1.01 (0.98-1.04, p=0.447)
Transfusion requirement PLT (U)	1.08 (1.05-1.12, p<0.001)	1.08 (1.01-1.14, p=0.018)	1.04 (1.02-1.05, p<0.001)	1.03 (1.00-1.05, p=0.082)
Complex Karyotype	4.53 (0.46-45.16, p=0.198)	1.03 (0.06-17.23, p=0.986)	10.80 (1.45-80.23, p=0.020)	6.01 (0.72-50.19, p=0.098)
Relapsed/Refractory	2.67 (1.53-4.67, p<0.001)	1.79 (0.87-3.70, p=0.115)	2.25 (1.58-3.21, p<0.001)	1.68 (1.15-2.44, p=0.007)
Treatment Discontinuations	2.25 (1.02-4.92, p=0.043)	1.32 (0.49-3.53, p=0.587)	1.59 (0.97-2.60, p=0.065)	1.09 (0.65-1.83, p=0.737)
Co-occurring mutations				
ASXL1	0.97 (0.42-2.24, p=0.947)		0.94 (0.55-1.60, p=0.810)	
BCOR/BCORL1	1.37 (0.54-3.46, p=0.503)		0.94 (0.53-1.68, p=0.843)	
CEBPA	0.63 (0.28-1.40, p=0.258)		0.52 (0.27-0.98, p=0.045)	0.58 (0.28-1.18, p=0.130)
DNMT3A	0.92 (0.44-1.91, p=0.814)		1.03 (0.63-1.68, p=0.906)	
EZH2	0.19 (0.02-1.47, p=0.111)	0.16 (0.01-2.24, p=0.172)	1.17 (0.57-2.41, p=0.664)	
FLT3/FLT3-ITD/FLT3-TKD	1.15 (0.61-2.16, p=0.667)		1.08 (0.71-1.64, p=0.704)	
GATA2	0.38 (0.11-1.35, p=0.136)	0.39 (0.06-2.66, p=0.339)	0.65 (0.29-1.48, p=0.304)	
IDH1/IDH2	0.46 (0.22-0.97, p=0.042)	0.68 (0.26-1.78, p=0.429)	0.86 (0.55-1.36, p=0.517)	
JAK2	1.47 (0.40-5.36, p=0.561)		1.24 (0.51-3.05, p=0.633)	
KIT	0.23 (0.03-1.85, p=0.168)	0.73 (0.07-8.18, p=0.800)	0.66 (0.21-2.08, p=0.477)	
KRAS/NRAS/PTPN11	1.07 (0.57-2.01, p=0.825)		0.93 (0.61-1.42, p=0.741)	
NPM1	0.58 (0.25-1.33, p=0.195)	0.93 (0.29-3.04, p=0.909)	0.72 (0.41-1.26, p=0.253)	
RUNX1	0.89 (0.40-1.96, p=0.770)		1.09 (0.67-1.78, p=0.723)	
SF3B1	0.93 (0.23-3.68, p=0.913)		1.13 (0.50-2.57, p=0.770)	
SRSF2	0.71 (0.19-2.70, p=0.617)		0.87 (0.35-2.13, p=0.758)	
TET2	1.22 (0.56-2.70, p=0.617)		0.99 (0.59-1.65, p=0.955)	
TP53	4.23 (1.76-10.17, p=0.001)	3.93 (0.89-17.30, p=0.071)	4.17 (2.55-6.81, p<0.001)	2.94 (1.37-6.30, p=0.005)
U2AF1	2.30 (0.83-6.37, p=0.109)	1.59 (0.38-6.59, p=0.526)	0.81 (0.38-1.74, p=0.594)	
WT1	1.01 (0.40-2.59, p=0.980)		1.14 (0.63-2.08, p=0.660)	

Values are n (%) or median (range);CI,confidence interval; ELN,European Leukemia Net;HR hazard ratio; IC,intensive chemotherapy; OR, odds ratio;VEN, venetoclax;FAB (French, American, British),myelodysplastic syndrome or myeloproliferative neoplasm (MDS/MPN); Hb,Hemoglobin; PLT, platelet.

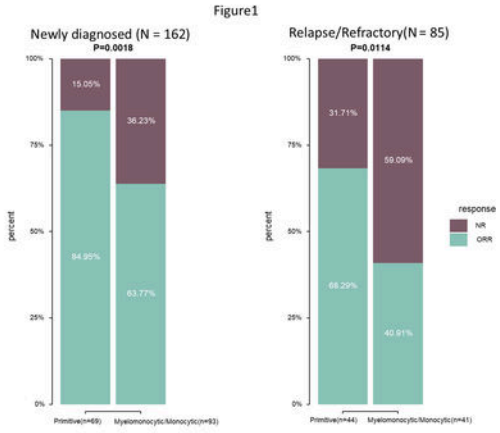

Figure 1

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