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ORAL ABSTRACTS

906.OUTCOMES RESEARCH-MYELOID MALIGNANCIES

Psychiatric and Substance Use Disorders Are Independent Predictors of Treatment Response and Outcomes in United States Veterans with Newly Diagnosed Acute Myeloid Leukemia Treated with Venetoclax Combinations

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BACKGROUND: Venetoclax (VEN) combinations have become the standard frontline therapy for patients with newly diagnosed acute myeloid leukemia (AML) who are deemed unable to tolerate intensive induction chemotherapy, either due to age or comorbidities. However, outcomes in the real-world setting have been inferior to those observed in clinical trials. Pre-existing psychiatric diagnoses and substance use disorders (SUDs) have previously been associated with increased mortality in patients with cancer, but their prognostic influence in veterans with AML is unclear. The aim of this study was to measure the prevalence of psychiatric and SUDs in veterans with AML treated with VEN combinations, determining the impact of these conditions on treatment response and outcomes.

METHODS: This was a retrospective cohort study of veterans with newly diagnosed AML who received frontline therapy with VEN combinations within the national Veterans Affairs (VA) Healthcare System. To measure the prevalence of psychiatric and SUDs, we used the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Data Warehouse algorithm, which tracks health conditions by administrative claims data with International Classification of Diseases (ICD) diagnostic and procedural codes. Our endpoints were rates of complete remission or complete remission with incomplete marrow recovery (CR/CRi), early mortality (EM, or death within 60 days of treatment initiation), intensive care unit (ICU) admissions, and overall survival (OS). We evaluated the relationship between comorbid medical conditions and outcomes using Kaplan-Meier analysis and Cox proportional hazards regression models, first unadjusted, and then adjusted for all covariates. Patients who underwent allogeneic stem cell transplantation (HSCT) were excluded from statistical analyses.

RESULTS: We identified 452 veterans treated with VEN up to April 1, 2022 (Table 1). In combination with VEN, 60% (n=270) received azacitadine, 37% (n=168) received decitabine, and 3% (n=14) received low-dose cytarabine. Median age was 74.3 years (IQR: 71.2-78.5) with 52% ≥75 years. By European LeukemiaNet (ELN) 2017 risk classification, 61% (n=274) were classified as adverse risk. Forty-six percent (n=206) of veterans had a preexisting psychiatric diagnosis, and 19% (n=84) had SUDs; 11% (n=49) had both comorbidities. Psychiatric disorders were significantly more prevalent in younger veterans (68% in <65 years vs 50% in 65-74 years vs 39% in ≥75 years, $p<0.003$); same was true for SUDs (38% in <65 years vs 26% in 65-74 years vs 9% in ≥75 years, $p<0.001$). For the entire cohort, CR/CRi was achieved by 57% (n=257), and only 3% (n=12) received HSCT. Zero veterans with SUDs and 8 with psychiatric diagnoses were transplanted. At the end of study period, 69% (n=310) had died. Median OS was 216 days (95% CI: 195-254). The 60-day mortality rate was 20% (n=87), of which 8 veterans had primary refractory AML. ICU admissions after treatment initiation was significantly higher in veterans with SUDs compared to those without history of SUDs (5.0 versus 2.2 per 5 person-years, $p<0.001$). On multivariable analyses (Table 2), both psychiatric and SUDs were independently associated with decreased odds of CR/CRi. Veterans with psychiatric disturbances had a 1.97 times

higher hazard of EM (95% CI: 1.16-3.39, p=0.01) and a 1.28 times higher hazard of death (95% CI: 1.00-1.64, p=0.05) compared to veterans without concurrent psychiatric disorders.

CONCLUSION: Psychiatric diagnoses and SUDs were not only prevalent among veterans with AML, but they also negatively impacted treatment response, EM, and OS-independently of age, sociodemographic variables, markers of disease risk, and VEN combination. Veterans with SUDs also had significantly higher ICU admissions after treatment initiation for AML. Compared to published clinical trials data, veterans experienced inferior outcomes. Veterans with psychiatric and SUDs may have difficulty adhering to regimens, reemergence of their mental instability and illness that is triggered by AML diagnosis and its treatment, or biologic mechanisms associated with these comorbidities. Better understanding of these factors contributing to health disparities and targeting these comorbidities with supportive care interventions alongside AML-specific therapy may improve outcomes and warrant further study.

Disclosures Hobbs: *Incyte:* Research Funding; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Keros:* Membership on an entity's Board of Directors or advisory committees; *Pharmaxis:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Morphosys:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Protagonist:* Membership on an entity's Board of Directors or advisory committees; *Regeneron:* Current holder of *stock options* in a privately-held company.

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Table 1. Baseline patient characteristics of veterans with AML treated with frontline venetoclax combinations

Patient characteristics	All patients (N= 452)
Age, median [IQR]	74.3 [71.2, 78.5]
<65 years, N (%)	34 (7.5)
65-74 years, N (%)	184 (40.7)
≥75 years, N (%)	234 (51.8)
Male, N (%)	445 (98.5)
Race/ethnicity, N (%)	
White	343 (75.9)
Black	47 (10.4)
Hispanic	23 (5.1)
Other/unknown	39 (8.6)
Rurality, N (%)	
Urban	291 (64.4)
Rural	153 (33.8)
Highly rural	6 (1.3)
Therapy-related AML, N (%)	27 (6.0)
Prior MDS/CMML/MPN, N (%)	162 (35.8)
Prior treatment with HMA, N (%)	56 (12.4)
ELN 2017 risk category, N (%)	
Favorable	27 (6.0)
Intermediate	100 (22.1)
Adverse	274 (60.6)
Venetoclax combination, N (%)	
Azacitadine	270 (59.7)
Decitabine	168 (37.2)
Low-dose cytarabine	14 (3.1)
Bone marrow blast >30%, N (%)	250 (55.3)
FLT3-ITD/TKD, N (%)	43 (9.5)
NPM1 mutation, N (%)	27 (6.0)
IDH1 mutation, N (%)	24 (5.1)
IDH2 mutation, N (%)	41 (9.1)
TP53 mutation, N (%)	56 (12.4)
ASXL1 mutation, N (%)	66 (14.6)
RUNX1 mutation, N (%)	67 (14.8)
HSCT, N (%)	12 (2.7)
Comorbidity†, N (%)	
Substance use disorders	83 (18.4)
Psychiatric disorders	206 (45.6)

†Substance use disorders included alcohol use disorder and drug use disorder. Psychiatric disorders included anxiety, bipolar disorder, depression/depressive disorders, personality disorder, post-traumatic stress disorder, schizophrenia, schizophrenia/related psychotic disorders. AML = acute myeloid leukemia, MDS = myelodysplastic syndromes, CMML = chronic myelomonocytic leukemia, MPN = myeloproliferative neoplasms, HMA = hypomethylating agent, ELN= European LeukemiaNet, HSCT = allogeneic stem cell transplantation.

Table 2. Multivariable Cox proportional hazards regression models* estimating association of psychiatric and substance use disorders with treatment response and outcomes in veterans with AML

	Substance Use Disorders (N = 83)	Psychiatric Disorders (N = 206)
CR/CRi† OR (95% CI)	0.47 (0.25-0.87)	0.52 (0.32-0.84)
CR/CRi, p-value	0.02	0.01
Early Mortality, HR (95% CI)	1.6 (0.83-3.03)	1.97 (1.16-3.39)
Early Mortality, p-value	0.15	0.01
OS, HR (95% CI)	1.34 (0.98-1.85)	1.28 (1-1.64)
OS, p-value	0.07	0.05

*Models were adjusted for age, gender, race/ethnicity, European LeukemiaNet (ELN) 2017 risk classification, bone marrow blast percent, AML type (de novo vs secondary), prior treatment with hypomethylating agent, and venetoclax combination. †Complete remission or complete remission with incomplete marrow recovery (CR/CRi) analysis excluded 51 who had missing response. AML = acute myeloid leukemia, OS = overall survival, OR = odds ratio, HR = hazard ratio, CI = confidence interval.

Figure 1