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V-RULES: Impact of Treatment Setting on CPX-351 Safety and Effectiveness in Secondary Acute Myeloid Leukemia

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Background

- Patients with acute myeloid leukemia (AML) have traditionally received intensive chemotherapy (IC) in the inpatient setting due to the need for continuous infusion and close monitoring of potential IC-related toxicities, resulting in substantial healthcare resource utilization (HCRU)[1-3]
  - Conventional 7+3 chemotherapy is administered as 7 days continuous infusion of cytarabine + 3 days of once-daily injections of an anthracycline,[4] whereas CPX-351 is administered as one 90-minute infusion (on days 1, 3, and 5 for first induction and days 1 and 3 for subsequent cycles), and, therefore, may be more amenable to administration in an outpatient setting[1,5,6]
- HCRU analyses of the CPX-351 vs 7+3 pivotal phase 3 trial in older adults with newly diagnosed high-risk or secondary AML showed that CPX-351, in addition to significantly improving overall survival and remission rate vs 7+3, was associated with shorter hospital stays and comparable supportive care use[1,6]
- Similarly, the real-world CREST-UK study reported that outpatient treatment with CPX-351 was feasible for all treatment stages, with the outpatient setting associated with a reduced need for hospital treatment in the UK healthcare system[7]
- The Vyxeos® Real-world US Long-term Effectiveness and Safety (V-RULES) study highlighted the real-world effectiveness and safety of CPX-351 in US patients with newly diagnosed secondary AML,[8] and provides an opportunity to explore real-world CPX-351 HCRU within the US healthcare system

Objective

- To report hospitalization incidence and duration, and safety of CPX-351 by treatment setting (inpatient vs outpatient) in the V-RULES study

Methods

- V-RULES was a retrospective, multicenter, single-arm, observational study
  - Pseudonymized data were collected from medical records of eligible patients with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC; according to the World Health Organization criteria 2016 or 2022) who received ⩾1 infusion of CPX-351 monotherapy in routine practice between October 26, 2017, and May 29, 2024, at 10 US centers
- Patient selection for delivery setting and dosing schedules were based on local decisions and policies
- Safety was assessed by delivery setting during first induction, and also after first induction for patients who received ⩾2 CPX-351 cycles to align and compare with the CREST-UK study[7]
- Descriptive statistics were used to report HCRU and safety by delivery setting (inpatient vs outpatient)
- The study was designed to be descriptive, without hypothesis testing

Results

Table 1. Baseline Patient and Disease Characteristics in the Overall V-RULES Population

	Overall (N=161)
Age at AML diagnosis	
Median, years (range)	60 (21, 78)
<60 years, n (%)	78 (48)
⩾60 years, n (%)	83 (52)
Male,[a] n (%)	94 (58)
Race,[b] n (%)	
American Indian or Alaska Native	1 (0.6)
Asian	5 (3)
Black or African American	21 (13)
White	116 (73)
Other	15 (9)
Ethnicity, n (%)	
Hispanic or Latino	18 (11)
Not Hispanic or Latino	136 (84)
Unknown	7 (4)
ECOG PS,[c] n (%)	
0	37 (28)
1	78 (60)
2	13 (10)
3	3 (2)
Missing, n	30
AML subtype, n (%)	
t-AML	47 (29)
AML-MRC	114 (71)
Prior MDS[d]	32 (28)
Prior CMML[d]	4 (4)
MDS-related cytogenetic abnormalities[d]	69 (60)
Multilineage dysplasia alone[d]	9 (8)
Grimwade cytogenetic classification,[e] n (%)	
Favorable	9 (6)
Intermediate	57 (37)
Adverse	88 (57)
Molecular abnormalities, n (%)	
TP53 mutation[f]	33 (25)
MDS-related gene mutations[g]	57 (63)
Charlson Comorbidity Index, mean (range)	1 (0, 12)

Percentages may not add to 100% due to rounding.
[a]Biological sex; [b]Multi-response question; 5 patients had missing data for race. Percentages were calculated out of total number of patients with non-missing data; [c]Percentages were calculated out of total number of patients with non-missing data; [d]Percentages were calculated out of 114 patients with AML-MRC; [e]7 patients had missing data for Grimwade cytogenetic classification. Percentages were calculated out of total number of patients with non-missing data; [f]27 patients had missing data for mutated *TP53*. Percentages were calculated out of total number of patients with non-missing data; [g]MDS-related mutations were defined as mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2*. Percentage was calculated out of 91 patients with data collected for MDS-related mutations.
AML, acute myeloid leukemia; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MDS, myelodysplastic syndrome; t-AML, therapy-related acute myeloid leukemia; *TP53*, tumor protein p53; V-RULES, Vyxeos Real-world US Long-term Effectiveness and Safety.

- In V-RULES, 161 patients (t-AML: 47/161 [29%]; AML-MRC: 114/161 [71%]) received between ⩾1 and ⩽4 cycle(s) of CPX-351
  - Median follow-up time was 9.7 months (quartile 1, quartile 3: 4.1, 27.8)
- During first induction, 134 patients and 27 patients were treated with CPX-351 as inpatients and outpatients, respectively
- Overall, 64 patients received ⩾2 cycles of CPX-351: after first induction, 43 patients received ⩾1 subsequent cycle(s) as outpatients, and 21 patients received all subsequent cycles as inpatients

Table 2. Hospitalization Incidence and Duration by Delivery Setting During CPX-351 Induction and Consolidation

	Overall	Inpatients	Outpatients	Outpatients Who Required Hospitalization
Induction 1				
Number of patients, n (%)	161 (100)	134 (83)	27 (17)	20 (74)
Days in ward, median (Q1, Q3)	32 (22, 40)[a]	33 (26, 41)	22 (0, 34)[a]	26 (22, 34)[a]
Induction 2				
Number of patients, n (%)	19 (100)	17 (89)	2 (11)	1 (50)
Days in ward, median (Q1, Q3)	32 (4, 43)	33 (28, 43)	5 (0, 10)	10 (10, 10)
Consolidation 1				
Number of patients, n (%)	50 (100)	9 (18)	41 (82)	10 (24)
Days in ward, median (Q1, Q3)	0 (0, 4)	8 (6, 27)	0 (0, 0)	4 (3, 16)
Consolidation 2				
Number of patients, n (%)	10 (100)	1 (10)	9 (90)	2 (22)
Days in ward, median (Q1, Q3)	0 (0, 4)	45 (45, 45)	0 (0, 0)	8 (4, 11)

[a]Data were missing for 1 patient.
Q1, quartile 1; Q3, quartile 3.

- For all stages of treatment with CPX-351, patients treated in the outpatient setting had shorter hospital stays compared with patients treated in the inpatient setting
- Patients who received outpatient treatment with CPX-351 spent a median of 11, 28, 8, and 45 days fewer on the ward compared with inpatient administration during first induction (n=27), second induction (n=2), first consolidation (n=41), and second consolidation (n=9), respectively
- Regardless of treatment setting, no patients required intensive care unit (ICU) support during first induction, second induction, or first consolidation; during second consolidation, 2 patients initially treated as outpatients required ICU support (median of 4 days in ICU)

Table 3. Safety by Delivery Setting During First Induction

	Inpatient (n=134)				Outpatient (n=27)			
	Grades 3-5	Grade 3	Grade 4	Grade 5	Grades 3-5	Grade 3	Grade 4	Grade 5
TEAE,[a] n (%)								
Bleeding	9 (7)	8 (6)	0	1 (1)	2 (7)	2 (7)	0	0
Febrile neutropenia	56 (42)	56 (42)	0	0	9 (33)	7 (26)	2 (7)	0
Gastrointestinal toxicity	13 (10)	13 (10)	0	0	1 (4)	1 (4)	0	0
Infection	28 (21)	21 (16)	6 (4)	1 (1)	3 (11)	3 (11)	0	0
Bacteremia	6 (4)	5 (4)	1 (1)	0	3 (11)	3 (11)	0	0
Cellulitis	7 (5)	7 (5)	0	0	0	0	0	0
Sepsis	15 (11)	10 (7)	4 (3)	1 (1)	0	0	0	0
Treatment-related TEAE, n (%)								
Pericarditis, myocarditis, endocarditis, cardiomyopathy, arrythmias, or other rhythm abnormalities	9 (7)	8 (6)	0	1 (1)	3 (11)	3 (11)	0	0
Newly developed arrhythmias	3 (2)	3 (2)	0	0	2 (7)	2 (7)	0	0

[a]Adverse event subtypes reported occurred in >5% of patients in either patient group.
TEAE, treatment-emergent adverse event.

- During first induction, compared with patients treated in the inpatient setting, the rates of grade ⩾3 treatment-emergent adverse events (TEAEs) in the outpatient setting were lower

Table 4. Safety by Delivery Setting After First Induction

	Inpatient (n=21)				Outpatient (n=43)			
	Grades 3-5	Grade 3	Grade 4	Grade 5	Grades 3-5	Grade 3	Grade 4	Grade 5
TEAE,[a] n (%)								
Bleeding	5 (24)	4 (19)	0	1 (5)	6 (14)	6 (14)	0	0
Febrile neutropenia	7 (33)	7 (33)	0	0	20 (47)	20 (47)	0	0
Gastrointestinal toxicity	2 (10)	2 (10)	0	0	5 (12)	5 (12)	0	0
Infection	14 (67)	9 (43)	5 (24)	0	17 (40)	15 (35)	1 (2)	1 (2)
Bacteremia	1 (5)	1 (5)	0	0	8 (19)	7 (16)	1 (2)	0
Cellulitis	2 (10)	2 (10)	0	0	5 (12)	5 (12)	0	0
Colitis	4 (19)	4 (19)	0	0	2 (5)	2 (5)	0	0
Pneumonia	4 (19)	3 (14)	1 (5)	0	2 (5)	2 (5)	0	0
Sepsis	9 (43)	5 (24)	4 (19)	0	6 (14)	5 (12)	0	1 (2)
Treatment-related TEAE, n (%)								
Pericarditis, myocarditis, endocarditis, cardiomyopathy, arrythmias, or other rhythm abnormalities	2 (10)	2 (10)	0	0	1 (2)	1 (2)	0	0

[a]Adverse event subtypes reported occurred in >5% of patients in either patient group.
TEAE, treatment-emergent adverse event.

- After first induction, compared with patients treated in the inpatient setting, the rates of grade ⩾3 TEAEs of bleeding and infection in the outpatient setting were lower

Conclusions

- In the V-RULES study, outpatient delivery of CPX-351 in the US was feasible, especially during consolidation, with a reduction in hospitalization incidence and duration, and did not appear to be associated with increased adverse events compared with inpatient treatment
- These results are consistent with those observed in the UK healthcare system from the CREST-UK study and highlight important potential resource benefits of outpatient CPX-351 treatment[7]
- Together, the data from the V-RULES and CREST-UK studies reinforce the outpatient results from post hoc analyses of the CPX-351 phase 3 trial[1,6]
- The V-RULES findings provide insights into real-world use of CPX-351 in US patients with t-AML or AML-MRC, highlighting an opportunity for outpatient treatment for some patients

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