

Ten-day Decitabine with Venetoclax vs. Intensive Chemotherapy in Relapsed or Refractory Acute Myeloid Leukemia: A Propensity Score Matched Analysis

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ABSTRACT

Background: R/R AML has poor outcomes. It is unknown how HMA+VEN compares to intensive chemotherapy (IC) in the salvage setting.

Methods: We compared outcomes of R/R AML treated with 10-day decitabine and venetoclax (DEC10-VEN) vs. IC-based regimens. Propensity scores were used for matching patients to minimize bias.

Results: 65 pts in DEC10-VEN cohort were matched to 130 IC recipients. Median age for DEC10-VEN and IC groups were 64 and 58 years, respectively, and baseline characteristics were balanced. DEC10-VEN conferred significantly higher responses compared to IC including higher ORR (60% vs 36%, odds ratio [OR]= 3.28, p<.001), CRi (19% vs 6%, OR 3.56, p=.012), MRD-negative by flow cytometry (28% vs 13%, OR 2.48, p=.017) and lower rates of refractory disease. DEC10-VEN led to significantly longer median EFS compared to IC (5.7 vs 1.5 months, HR=0.46, 95%CI 0.30-0.70, p<.001) as well as median OS (6.8 vs 4.7 months, HR=0.56, 95%CI 0.37-0.86, p=.008). DEC10-VEN was independently associated with improved OS compared to IC in multivariate analysis. Exploratory analysis for OS in 27 subgroups showed that DEC10-VEN was comparable to IC for R/R AML

Conclusion: DEC10-VEN may offer better responses and survival compared to IC in adults with R/R AML.

BACKGROUND

- HMA-VEN is the current standard for older/unfit pts with newly diagnosed AML.¹
- There are no standard salvage therapies for R/R AML in the absence of actionable mutations.
- DEC10-VEN is an active regimen for R/R AML and potentially better than IC in frontline setting.^{2,3}
- However, it is unknown how DEC10-VEN compares to IC in salvage setting.

METHODS

We included pts with R/R AML, treated with –

- DEC10-VEN**
 - DEC 20 mg/m² x 10 days every 4-8 weeks
 - Consolidation/maintenance: DEC x5d post CR/CRi
 - VEN D1-21/28 for cycle 1 → D1-21 cycle 2 onward
 - FLT3i, BCR-ABL TKIs allowed
- Intensive chemotherapy (IC)**
 - IA, CLIA, CIA, FIA or FLAG-Ida-based regimens without venetoclax, with or without additional agents on phase 1b/2 clinical trials or as SOC.

METHODS

Response Assessment

- Outcomes assessed per ELN2017, CTCAE v4.0
- Measurable residual disease assessed by flow cytometry (0.1-0.01%)

Statistical Analysis

- Propensity scores calculated by logistic regression using baseline characteristics including –
- Age, ECOG PS, no. of prior therapies, primary refractory vs relapsed disease, CR1 duration, prior SCT, ELN cytogenetics, *FLT3* and *TP53*
- Propensity score matching with the nearest neighbor method used to select the IC comparison group using 1:2 matching
- Stratified log-rank test and Cox PH model with stratification for matched pairs used to compare groups.

RESULTS

Table 1. Baseline characteristics

Patient characteristics	DEC10-VEN (N=65)	IC (N=130)	<i>p</i>
Age, years	64 [18-85]	58 [19-80]	.113
Male sex	39 (60)	72 (55)	.539
AML type			
Primary refractory AML	28 (43)	54 (42)	
Relapsed AML	37 (57)	76 (58)	.837
sAML from AHD	11 (17)	21 (16)	.891
ECOG PS ≥2	19 (29)	35 (27)	.734
Bone marrow blasts, %	34 [1-96]	35 [0-98]	.536
ELN 2017 cytogenetics			
Intermediate	41 (63)	80 (62)	.958
Adverse	24 (37)	50 (38)	
Mutations			
<i>NPM1</i>	14 (22)	15 (12)	
<i>FLT3</i> -ITD/TKD	16 (25)	34 (26)	
<i>IDH1/2</i>	11 (17)	28 (22)	.605
<i>TP53</i>	18 (28)	32 (25)	
<i>RUNX1</i>	12 (18)	22 (17) ¹	
<i>ASXL1</i>	10 (15)	14 (11) ¹	
ELN 2017 risk group			
Favorable	10 (15)	11 (8)	
Intermediate	12 (18)	30 (23)	.302
Adverse	43 (66)	89 (68)	
Prior therapies	2 [1-8]	2 [1-10]	.721
HMA only	16 (25)	24 (18)	
IC only	31 (48)	53 (41)	.214
IC and HMA	16 (25)	53 (41)	
SCT	18 (28)	36 (28)	

Results reported as n (%), or median [range]. AHD = antecedent hematological disorder, ELN = European LeukemiaNet. IC = intensive chemotherapy, HMA = hypomethylating agent, SCT = allogeneic stem cell transplantation. 1. *RUNX1* and *ASXL1* status was unknown for 9 pts.

RESULTS

- DEC10-VEN cohort - pt received a median of 2 cycles (range 1-16)
- IC cohort – pts received a median of 1 cycle (range 1-5).
- FLT3i used in 16/16 pts in DEC10-VEN vs. 25/34 pts in IC group (p=.043).
- No patients received IDH1/2 inhibitors.

Table 2. Outcomes with DEC10-VEN vs Intensive chemotherapy

Outcomes	DEC10-VEN (N=65)	IC (N=130)	OR / HR (95% CI)	Strati-fied <i>p</i>
ORR	37 (60)	36 (28)	3.28 (1.73, 6.23)	<.001
CR/CRi	27 (42)	30 (23)	2.52 (1.26, 5.03)	.009
CR	15 (23)	22 (17)	1.44 (0.70, 2.94)	.320
CRi	12 (19)	8 (6)	3.56 (1.32, 9.61)	.012
MLFS	10 (15)	6 (5)	3.33 (1.21, 9.17)	.020
MRD negativity	18 (28)	17 (13)	2.48 (1.17, 5.24)	.017
Refractory	22 (35)	71 (55)	0.46 (0.25, 0.84)	.011
Relapse	19 (51)	17 (47)	0.75 (0.24, 2.38)	.630
60-day mortality	8 (12)	35 (27)	0.40 (0.18, 0.91)	.029

Results reported as n (%), n/N (%). ORR = CR+CRi+MLFS, OR = odds ratio; HR = hazard ratio.

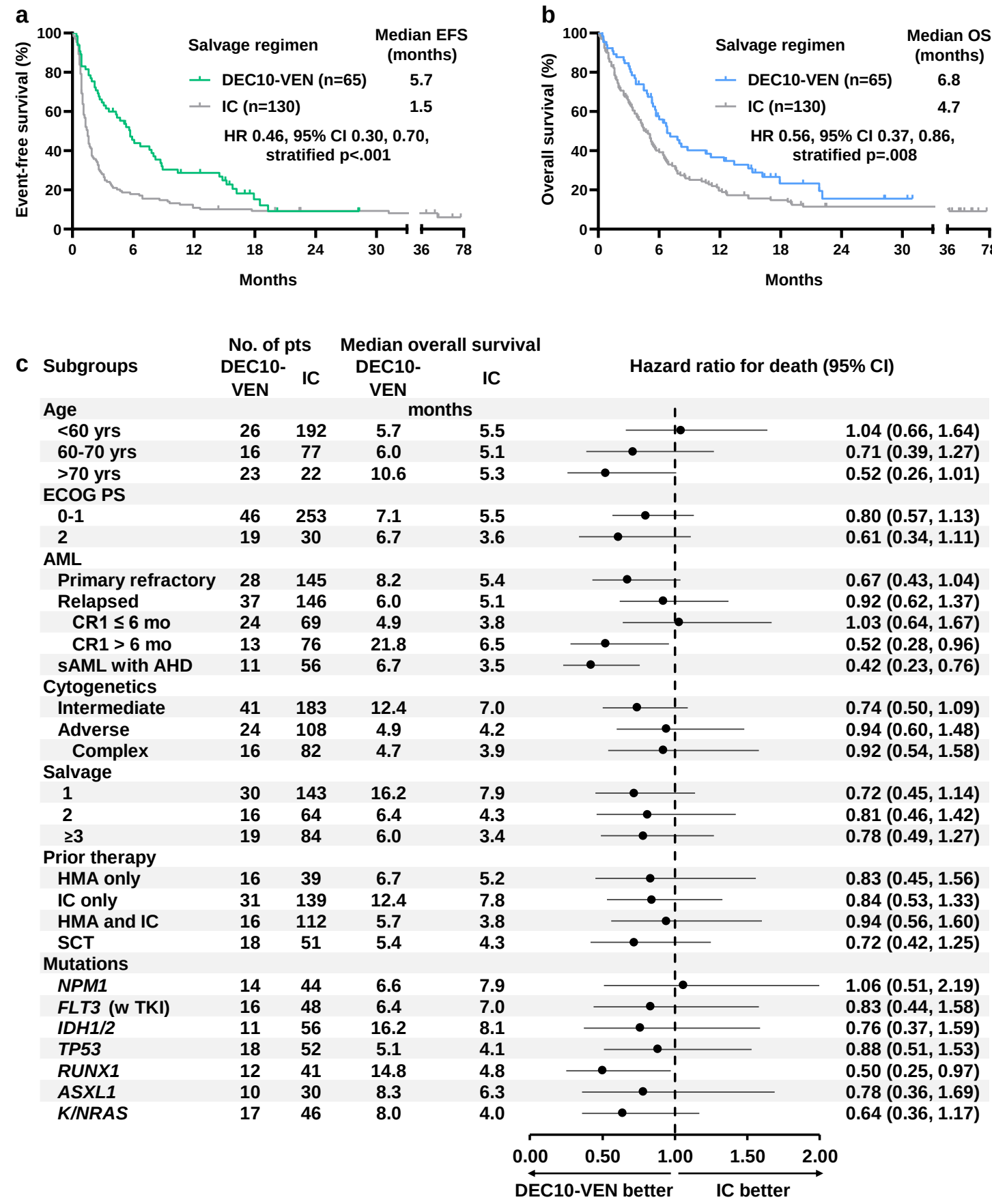
Table 3. TEAE with DEC10-VEN, regardless of attribution.

Event	DEC10-VEN (n=65)		IC (n=28)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Infection w ANC <1.0x10 ⁹ /L	25 (38)	25 (38)	6 (21)	5 (17)
Febrile neutropenia	20 (30)	20 (30)	14 (50)	14 (50)
Infection w ANC >1.0x10 ⁹ /L	14 (21)	11 (16)	3 (10)	3 (10)
Mucositis	4 (6)	..	4 (14)	1 (3)
Hyperbilirubinemia	3 (4)	3 (4)	8 (28)	2 (7)
Nausea	3 (4)	..	1 (3)	..
Tumor lysis syndrome	3 (4)	1 (1)	1 (3)	1 (3)
Constipation	2 (3)	..	..	..
Renal Failure	2 (3)	2 (3)	..	..
Pain	1 (1)	1 (1)	4 (14)	2 (7)
Hypokalemia	1 (1)	..	..	..
Vomiting	1 (1)	..	..	..
ALT/AST elevation	..	..	10 (35)	1 (3)
Hemorrhage	..	..	4 (14)	3 (10)
Rash	..	..	4 (14)	..
Creatinine elevation	..	..	3 (10)	..
Altered mental status	..	..	1 (3)	1 (3)
Cardiac arrhythmia	..	..	1 (3)	..
Cholecystitis	..	..	1 (3)	1 (3)
Dyspnea	..	..	1 (3)	1 (3)
Hypoxia	..	..	1 (3)	1 (3)

ANC = absolute neutrophil count, ALT = alanine aminotransferase, AST = aspartate aminotransferase

RESULTS

Fig. 1a. Event-free survival (EFS), **b.** overall survival (OS) in pts with R/R AML who received salvage therapy with DEC10-VEN vs. IC; and **c.** exploratory subgroup analysis for OS



- 15 pts (23%) in DEC10-VEN cohort and 21 pts (16%) in the matched IC cohort received SCT after response (p=.247).
- Median OS after SCT was numerically longer in DEC10-VEN vs IC cohorts (18.7 vs 12.9 months, HR 1.11, 95% CI 0.44, 2.84, p=.813)
- Pts with *FLT3*^{mut} AML treated with DEC10-VEN and FLT3 inhibitor (n=16) versus IC with FLT3 inhibitor (n=48) had comparable OS (6.4 vs 7.0 mo, HR 0.83, 95% CI 0.44, 1.58, p=0.587).

RESULTS

Multivariate analysis for OS

- DEC10-VEN was independently associated with significant improvement in OS (HR 0.66, 95% CI 0.48, 0.92, p=.012)

Toxicity

- Non-hematologic grade 3/4 treatment-emergent adverse events (TEAE), at least possible related to study regimen, occurred in 21/28 (75%) pts receiving IC and 45/65 (69%) pts receiving DEC10-VEN (p=.628).
- Grade 3/4 infectious AEs occurred in 25/65 (38%) pts in DEC10-VEN cohort vs 5/28 (18%) pts in IC (p=.057).
- Febrile neutropenia was noted in 20 pts (30%) in DEC10-VEN cohort vs. 14 pts (50%) in IC cohort (p=.101).

CONCLUSIONS

- DEC10-VEN should be considered as a potential salvage option for R/R AML
- DEC10-VEN offers outcomes comparable to non-venetoclax based IC in R/R AML without prior venetoclax exposure.
- High ORR, rates of CRi, MLFS, MRD-negativity, better OS, EFS, and low-intensity nature makes this regimen a potential option as a bridge to SCT.
- Reasonable choice for a low-intensity backbone for adding novel therapies in the salvage setting.

Clinical trial registration: NCT03404193

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