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A Non-Cytotoxic Regimen Using Weekly Low Dose Decitabine and Venetoclax for MDS and AML in a Real World Cohort

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BACKGROUND

- Combination of hypomethylating agents and venetoclax (HMA/Ven) is currently the standard of care for treatment for patients with AML unfit for intensive induction chemotherapy.
- Despite increased tolerability, standard pulse-cycled stHMA/Ven frequently causes myelosuppression necessitating treatment interruptions and dose reductions in 72% of patients[1]
- Preclinical data demonstrate that DNMT-1 depletion occurs at HMA doses as low as <1um. Cancer cell adaptive metabolism confers resistance but can be inhibited by concurrent Ven administration.[2,3,4] Thus, metronomic weekly Ven dosing the day prior to HMA therapy is thought to selectively affect malignant clones while sparing normal hematopoiesis.

METHODS

Hypothesis: Patients with AML, MDS, CMML treated with once-a-week low-dose decitabine and venetoclax (LDDec/Ven) have comparable outcomes to patients treated with standard regimen of stHMA/Ven.

Study Design: Retrospective chart review of patients at Montefiore Medical Center, Bronx, NY between 11/2018 and 11/2022.

Primary Outcomes: 60-day mortality, time on treatment, and dose interruptions

Secondary Outcomes: Overall response rates (ORR), overall survival (OS), Event-Free Survival (EFS) as a composite of time to next therapy, progression of disease, death, or last follow-up.

RESULTS

Table 1. Response rates for AML and MDS patients.

	LDDec/Ven	stHMA/Ven	
AML 1st line, n	12	11	
CR/CRi (%)	5 (63)	6 (67)	P=0.68
ORR (%)	7 (88)	8 (89)	P=0.67
AML≥2nd line, n	7	21	
CR/CRi (%)	1 (17)	9 (50)	P=0.37
ORR (%)	5 (83)	14 (77)	P=1
MDS, N	16	4	
CR/Marrow CR	6 (55)	2 (50)	
ORR	7 (63)	2(5)	

CR, complete remission; CRi, complete remission with incomplete hematologic recovery; ORR, overall response rate

Time on treatment for AML patients

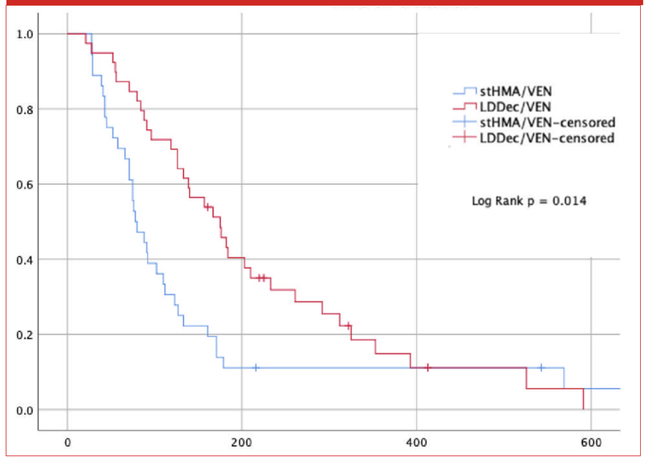


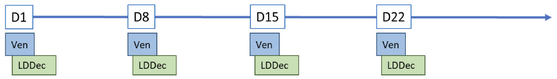
Table 2. Event free survival (EFS) and overall survival (OS) data.

AML 1st line	LDDec/Ven	stHMA/Ven	
EFS, median days	243	363	P=0.28
OS, median days	353	393	P=0.10
AML>2nd line			
EFS, median days	125	333	P=0.15
OS, median days	165	472	P=0.052

EFS defined as time to progression of disease, death, or change to next therapy.

TREATMENT SCHEMA

Ven: 400mg PO x1/week, the day before HMA
LDDec: 0.1-0.2mg/kg SQ 1- 2x/week



CONCLUSIONS

- This is the first report of outcomes of patients treated with once-weekly Low Dose Decitabine and Venetoclax schedule
- Therapy with LDDec/Ven, as opposed to standard HMA/Ven, results in significantly longer time-on-treatment with comparable response rates as well as trend to more transfusion independence
- A significant limitation of this presented study is population heterogeneity of non-randomized, retrospective cohorts
- A prospective clinical trial evaluating LDDec/Ven in MDS and AML (NCT05184842) is currently enrolling patients.

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