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Feasibility of Azacitidine and Venetoclax followed by High/Intermediate dose cytarabine (HIDAC/IDAC) consolidation in previously untreated acute myeloid leukemia patients unfit for intensive chemotherapy in a resource constraint low-middle income country- A Pilot Study

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INTRODUCTION

- Traditional AML treatment includes 3+7 induction followed by HI/IDAC consolidation.
- Venetoclax, a BCL-2 inhibitor, is effective in unfit AML patients.
- This study explores the feasibility of HIDAC/IDAC consolidation following Aza-Ven in ND, unfit AML patients, where long-term Venetoclax is impractical.

AIM

- **Primary Objective:**
- Assess overall survival (OS) and progression-free survival (PFS) in AML patients treated with azacitidine- venetoclax followed by HIDAC/IDAC consolidation.
- **Secondary Objectives:**
- Evaluate remission status post-induction and post-consolidation.
- Compare OS and PFS with continuous azacitidine- venetoclax therapy.
- Identify barriers to HI/IDAC consolidation post-remission.

METHOD

- **Study Design:** Ambispective, non-randomized interventional study.
- **Setting:** Department of Hematology, AIIMS, New Delhi.
- **Population:** Newly diagnosed, unfit AML patients (>18 years old) treated at AIIMS, excluding secondary AML
- **Duration:** 3.5 years (2 years retrospective + 1.5 years prospective).

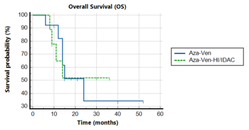
Procedure:

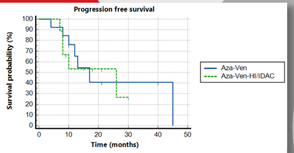
- Induction with azacitidine (75 mg/m²/day for 7 days) and venetoclax (dose-adjusted).
- Remission assessment after 2 cycles; fit patients receive HI/IDAC consolidation.
- Control arm: Continuous azacitidine- venetoclax therapy.
- **Outcomes:** Overall survival (OS), progression-free survival (PFS), and remission status will be tracked for 6 months post-therapy initiation.

RESULTS

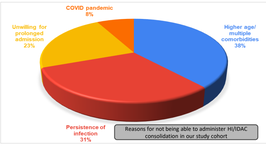
- Out of total 151 AML patients,104 were excluded, leaving 47 patients unfit for intensive chemotherapy.
- Of these 47, 25 patients did not achieve remission after two cycles, primarily due to induction mortality.
- The remaining 22 patients achieved remission with Azacitidine-Venetoclax (Aza-Ven); 9 received HIDAC/IDAC consolidation, while 13 continued Aza-Ven.
- The median age was 55 years; 42.5% were over 60 years old, with 94% having ECOG PS ≥ 2.
- Baseline infections were present in 75%, with 57% of these involving pneumonia, and 70% of pneumonia cases were fungal.
- The Aza-Ven-HIDAC group had a lower median age (44 vs. 60 years) but higher baseline infection rates (89% vs. 77%).
- No significant differences were found in OS and PFS between the groups, with a median OS of 24 months for Aza-Ven and was not reached for Aza-Ven-HIDAC.
- MRD negativity was achieved in 44% of the Aza-Ven-HIDAC group and 31% of the Aza-Ven group after further treatment.
- Overall relapse rates were 44% for Aza-Ven-HIDAC and 31% for Aza-Ven, with the median time to relapse being 9 and 11 months, respectively.
- There's significantly higher rate of transfusion requirements and duration of hospitalization in Aza-Ven-HIDAC group

Characteristics	Aza-Ven-HI/IDAC group (N=9)	Aza-Ven group(N=13)	P value
Age= Median (range)- year	44 (18-62)	60 (37-85)	0.06
Age ≥ 60 years - no. (%)	4 (44)	7 (54)	0.50
Male sex- no. (%)	4 (44)	9 (69)	0.384
Baseline infection- no. (%)	8 (89)	10 (77)	0.616
Baseline hyperleukocytosis	2 (22)	1 (8)	0.85
ECOG PS •1 •2 •≥3	 0 9 (100) 0	 1 (8) 9 (69) 3 (23)	 1 0.115 0.240
Hemoglobin (g/dL)- Mean (range)	7.8 (4.9-9.6)	8.5 (5.2-11.2)	0.051
Total leukocyte count (× 10³/µL) - Median (range)	5.3 (0.78-157)	5.8 (1.6-306)	0.695
Platelet count (× 10³/µL)	25 (10-156)	53.8 (6-168)	0.556
Baseline cytopenia grade ≥3 (CTCAE) •Anemia - no. (%) •Neutropenia - no. (%) •Thrombocytopenia - no. (%)	 7 (78) 5 (56) 6 (67)	 5 (38) 6 (46) 7 (54)	 0.099 1 0.20
Creatinine (mg/dL) - Mean (range)	1.1 (0.36-2.5)	0.9 (0.4-1.6)	0.948
Uric acid (mg/dL)	6 (1-8.2)	5.4 (2.6-8.1)	0.896
Total bilirubin (mg/dL)	0.9 (0.39-2.1)	1.26 (0.2-4.6)	0.001
Direct bilirubin (mg/dL)	0.5 (0.19-1.02)	0.58 (0.2-3)	0.697
ELN risk •Favorable •Intermediate •Adverse	 1 (11) 6 (67) 2 (22)	 1 (8) 5 (38) 7 (53)	 1 0.38 0.20





Groups	Median OS (months)	Median PFS (months)
Aza-Ven	14 (12.00 - 14.00)	13 months (8.00 - 13.00)
Aza-Ven-HI/IDAC	Not reached	26 months (7.00 - 26.00)
P Value	0.3495	0.5893



Reasons for not being able to administer HI/IDAC consolidation in our study cohort

Parameters	Aza-Ven group	Aza-Ven-HIDAC	P value
Duration of hospitalization in days- Median (Range)	54 (10 - 87)	98 (79 - 128)	0.000028
Transfusion requirements (numbers)- Mean (Range) •PRBC •SDP	 12.5 (8 - 18) 12 (9 - 25)	 17.6 (13 - 22) 18 (14 - 24)	 0.004 0.001
Deaths due to febrile neutropenia	2	2	1

Days of hospitalization, transfusion requirements and death due to febrile neutropenia in each group

CONCLUSIONS

- Infections, rather than age or comorbidities, were the primary reason for unfitness, contrasting with Western data.
- The overall remission rate was 47% with Aza-Ven therapy, with a high induction mortality of 38%, largely due to baseline infections.
- Post-remission therapy following Aza-Ven remains a challenge, with the study exploring the feasibility of HIDAC consolidation, though it did not show a significant survival advantage.
- HI/IDAC consolidation offers a cost-effective, time-limited option in LMICs.
- Larger studies with extended follow-up are needed to validate these findings.

REFERENCES

1. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N Engl J Med*. 2020;383(7):617-629. doi:10.1056/NEJMoa2012971
2. Samra B, Konopleva M, Isidori A, Daver N, DiNardo C. Vene toclax-based combinations in acute myeloid leukemia: current evidence and future directions. Front Oncol. 2020;10: 562558
3. Mirgh S, Sharma A, Shaikh MRMA, Kadian K, Agrawal N, Khushoo V, et al. Hypomethylating agents+venetoclax induction therapy in acute myeloid leukemia unfit for intensive chemotherapy—novel avenues for lesser venetoclax duration and patients with baseline infections from a developing country. Am J Blood Res. 2021;11(3):290–302

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