Comparing Intensive Purine Analogues Regimens with Cladribine and Fludarabine; CLIA-Venetoclax vs. FLAG-Ida-Venetoclax for Relapsed and Refractory AML During a Fludarabine Shortage

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Background

Intensive chemotherapy (IC) combinations with venetoclax are being used more frequently for acute myeloid leukemia (AML). In May 2022, a critical shortage of fludarabine prompted cladribine substitution at many institutions. FLAG-Ida-Ven (fludarabine, cytarabine, idarubicin, filgrastim, venetoclax) and CLIA-Ven (cladribine, cytarabine, idarubicin, venetoclax) are similar regimens using different purine analogues, potentially with different efficacy and toxicity.

Design

The objective was to describe the patient population, outcomes, and toxicities of patients receiving FLAG-Ida-Ven and CLIA-Ven.

A retrospective analysis of patients over 18 years with AML who received FLAG-Ida-Ven or CLIA-Ven for R/R AML at City of Hope National Medical Center between December 2020 and January 2023. Patients were identified in our EMR using an ICD-10 code for AML and documented administration of medications. Dosing of FLAG-Ida-Ven was per DiNardo et al from the R/R AML arm and CLIA-Ven from Kadia et al.

The primary outcome was composite CR (CRc) rate per modified International Working Group criteria. Measurable residual disease (MRD) by flow cytometry sent to University of Washington. Secondary outcomes included time to relapse, and non-hematologic toxicity.

Patient Characteristics

	FLAG-IDA-VEN (n=31)	CLIA-VEN (n=7)
Gender, n (%)		
• **Male**	21 (67)	4 (57)
Median age, yrs (range)	53 (20-78)	40 (23-69)
AML Type, n (%)		
• **De-Novo**	20 (65)	7 (100)
• **s-AML or t-AML**	10 (32)	0 (0)
• **CML Blast crisis transformation**	1 (3)	0 (0)
Median lines of therapy (range)	2 (1-7)	1 (1-2)
History of HSCT, n(%)	6 (19)	0 (0)
Prior venetoclax, n (%)	19 (61)	3 (42)
Median WBC on presentation, n (range)	1.8 (0.3-63.9)	8.9 (1-35.8)

Outcomes

	FLAG-IDA-VEN (n=31)	CLIA-VEN (n=7)
Duration of venetoclax during induction, n (%)		
• **7 days**	0 (0)	6 (86)
• **8-13 days**	7 (23)	0 (0)
• **14 days**	22 (71)	1 (14)
• **>14 days**	2 (6)	0 (0)
Overall Response Rate, n(%)	14/30 (46)	4/7 (57)
• **CR/CRi**	4/30 (13)	4/7 (57)
• **MLFS**	10/30 (33)	0/7 (0)
• **MRD-negative**	12/14 (86)	3/4 (75)
Hematologic count recovery		
Median ANC Recovery, days	35 (20-67)	34 (26-46)
Median Plt Recovery, days	38.5 (24-206)	28 (26-30)
Patients without Plt Recovery	13/31 (42)	4/6 (67)
Patients without ANC recovery	12/31 (39)	1/6 (17)
Consolidate with HCT, n (%)	13 (42)	3 (43)
Time to relapse, days	58 (23-91)	115 (111 – 119)

Safety Analysis

	FLAG-IDA-VEN (n=31)	CLIA-VEN (n=7)
Incidence of non-hematologic Grade 3 or 4 adverse event, n (%)	2 (6)	5 (71)
Hepatotoxicity, n (%)		
• **Hyperbilirubinemia**	0 (0)	1 (14)
• **Transaminitis**	0 (0)	3 (43)
Cardiac Disorders	2 (6)	4 (57)
Incidence of new bacterial infection, n (%)	5 (16)	4 (57)
30-day mortality, n (%)	1 (3)	0 (0)
90-day mortality, n (%)	10 (32)	1 (14)
6-month survival, n (%)	14 (45)	5 (71)

Results

The median age of patients receiving FLAG-Ida-Ven was 53 [20-78] compared to 40 [23-69] in the CLIA-Ven group, and most were male (67% vs. 57%). The majority in both groups had ELN adverse risk AML (20/31 and 5/7 patients). Patients in the FLAG-Ida-Ven group were more heavily pretreated with 2 median prior lines of treatment compared to 1 in CLIA-Ven. Prior exposure to venetoclax therapy was common (61% vs 42%). The ORR (overall response rate) was 46% and 57%, respectively, with 86% vs 75% achieving MRD negative remissions; CR/CRi rates were 13% vs 57% and MLFS was 33% vs 0%. The median time to relapse was 58 [23-91] vs 115 [111-119] days. CLIA-Ven had higher incidence of grade 3 or 4 non-hematologic adverse events, 6% vs 71%.

Conclusion

In this descriptive series of a relatively small number of patients, FLAG-Ida-Ven and CLIA-Ven had similar response rates, however CLIA-Ven may be associated with more toxicity.

References

1.DiNardo CD, Lachowiez CA, Takahashi K, et al. Venetoclax Combined With FLAG-IDA Induction and Consolidation in Newly Diagnosed and Relapsed or Refractory Acute Myeloid Leukemia. J Clin Oncol. 2021 Sep 1;39(25):2768-2778.

2.2. Kadia TM, et al. Venetoclax plus intensive chemotherapy with cladribine, idarubicin, and cytarabine in patients with newly diagnosed acute myeloid leukaemia or high-risk myelodysplastic syndrome: a cohort from a single-centre, single-arm, phase 2 trial. Lancet Haematol. 2021 Aug;8(8):e552-e561.