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615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Cladribine and Low-Dose Cytarabine-Based Salvage Therapy for Relapsed/Refractory AML in a Predominantly Venetoclax-Exposed Cohort

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Introduction: Relapsed/refractory acute myeloid leukemia (R/R AML) remains challenging to treat. Unfit patients receive either targeted therapy for actionable mutations or low-intensity chemotherapy, often a hypomethylating agent with venetoclax (HMA/ven). Aggressive regimens, such as a purine analog with high-dose cytarabine, are reserved for fit patients. A regimen using similar drug classes, comprised of cladribine (clad), low-dose cytarabine (LDAC), and venetoclax (clad/LDAC/ven), has demonstrated favorable efficacy and safety for frontline AML treatment in older patients, according to recent phase 2 studies [Kadia 2018 Lancet Hematology; Kadia 2022 Journal of Clinical Oncology]. Interestingly, monocytic differentiation is a proposed mechanism of venetoclax resistance, and monocytic leukemic stem cells rely on purine metabolism, thus suggesting unique cladribine sensitivity [Pei 2023 Cancer Discovery]. The utility of clad/LDAC with or without venetoclax in R/R AML is not well characterized, especially in today's evolving treatment landscape.

Methods: In this single-center retrospective cohort study, we report efficacy and safety outcomes of a salvage regimen using a clad/LDAC backbone in adult patients with R/R AML between 2019 and 2023. For induction, patients received cladribine 5 mg/m2 IV daily days 1 to 5 and cytarabine 20 mg/m2 IV daily days 1 to 10. A third agent, such as venetoclax at a target dose of 400 mg oral daily days 1 to 21, was added at the provider's discretion. Dose reductions were allowed based on performance status and organ function. Re-induction was considered if the bone marrow biopsy demonstrated inadequate response. Patients who responded received clad/LDAC-based consolidation or proceeded to allogeneic hematopoietic cell transplant (alloHCT).

Results: A total of 35 patients received clad/LDAC-based salvage induction for R/R AML. Median age was 68 years old, and patients had a median of 1 prior line of therapy. Half of patients had secondary AML, and most had adverse risk disease. The most common regimen received was clad/LDAC (49%), followed by clad/LDAC/ven (43%). Among 32 patients evaluable for response, the overall response rate (ORR) was 38%, with complete response (CR) of 16% and complete response with incomplete count recovery (CRi) of 22%. The median progression-free survival (mPFS) was 1.4 months (range 0.4-22.8), and median overall survival (mOS) was 3.4 months (range 0.4-22.8). At 6 months, PFS was 11% and OS was 26%. At 12 months, PFS was 11% and OS was 15%. For responders, 33% achieved negative measurable residual disease (MRD), 33% proceeded to alloHCT, mPFS was 3.3 months (range 0.9-22.8), and mOS was 6.4 months (0.9-22.8). Mutational profiling of responders revealed *ASXL1*, *CSF3R*, *NF1*, *SETBP1*, and *U2AF1* to be most the common. In a subgroup of 21 patients who had progressive or refractory disease with frontline HMA/ven, clad/LDAC-based salvage resulted in ORR 37%, CR 16%, CRi 21%, MRD negativity 57% among responders, mPFS 1.4 months (range 0.4-20.9), and mOS 2.3 months (range 0.4-21.8).

Clad/LDAC-based induction was well tolerated, with no cases of treatment-related mortality. Common adverse effects included febrile neutropenia (74%), grade 1 or 2 elevated bilirubin (49%), grade 1 transaminitis (48%), rash (43%), nausea/vomiting (37%), and grade 1 acute kidney injury (31%). One third of patients received clad/LDAC-based regimen in the outpatient setting.

Conclusions: Clad/LDAC and clad/LDAC/ven represent feasible salvage induction strategies for R/R AML that may be administered outpatient and associated with minimal toxicity. Favorable response rates occurred in a subgroup of patients who failed frontline HMA/ven, in which there is an unmet need.

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OffLabel Disclosure: Cladribine, low-dose cytarabine, and venetoclax for salvage AML induction

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Table 1: Baseline Characteristics and Treatment*

	N=35
Age (years)†	68 (42-87)
Performance status (ECOG)	
0	4 (11)
1	20 (57)
2	10 (29)
3	1 (3)
Baseline blasts (%)‡	
Bone marrow	29.3 (12.9, 76.8)
Peripheral blood	9 (4, 37)
Baseline WBC ($x10^9$/L)‡	2.3 (1.25, 1.45)
Diagnosis	
De novo AML	19 (54)
Therapy-related AML	3 (9)
AML from antecedent hematologic disorder	13 (37)
MDS	8 (23)
CMML	4 (11)
Myelofibrosis	1 (3)
Prior lines of treatment	
1	21 (60)
2	10 (29)
3 or more	4 (11)
Prior venetoclax exposure	29 (83)
Prior alloHCT	8 (23)
Disease status	
Refractory	17 (49)
Relapsed	18 (51)
Time from prior remission to relapse (months)†	3.7 (0.7-28)
ELN risk	
Favorable	4 (11)
Intermediate	11 (31)
Adverse	20 (57)
Cytogenetic group	
Favorable	2 (6)
Intermediate	25 (71)
Adverse	6 (17)
Insufficient metaphases	2 (6)
FAB classification	
M1 (AML without maturation)	1 (3)
M2 (AML with maturation)	1 (3)
M4 (acute myelomonocytic leukemia)	6 (17)
M5b (acute monocytic leukemia)	4 (11)
M6 (acute erythroleukemia)	1 (3)
Unknown	22 (63)
Clad/LDAC-based regimen received	
Clad/LDAC	17 (49)
Clad/LDAC/ATRA	1 (3)
Clad/LDAC/glasdegib	2 (6)
Clad/LDAC/venetoclax	15 (43)
Cycles received†	1 (1-15)
Dose reduction during induction	20 (57)

*Unless otherwise specified, results are reported as n (%); †median (range); ‡median (inter-quartile range)

Table 2: Efficacy of Cladribine and Low-dose Cytarabine-Based Salvage Induction*

	N=35
Evaluable for response	32 (91)
Overall response (CR/CRi) (among those evaluable for response)	12 (38)
CR	5 (16)
CRi	7 (22)
No response	20 (63)
MRD (among responders)	
Negative	4 (33)
Positive	4 (33)
Unknown	4 (33)
Subsequent alloHCT (among responders)	4 (33)
Time to achieving CR (days)†	37 (21-63)
PFS (months)†	1.4 (0.4-22.8)
OS (months)†	3.4 (0.4-22.8)
Median follow-up (months)†	3.4 (0.4-22.8)
6-month PFS	4 (11)
6-month OS	9 (26)
12-month PFS	4 (11)
12-month OS	5 (15)
Outcomes of frontline HMA/ven subgroup (n=21)	
Cycles of HMA/ven received†	4 (1-36)
Overall response with HMA/ven (CR/CRi)	9 (43)
CR	8 (38)
CRi	1 (5)
MLFS with HMA/ven	1 (5)
No response with HMA/ven	11 (52)
MRD with HMA/ven (among responders)	
Negative	5 (50)
Positive	4 (40)
Unknown	1 (10)
PFS with HMA/ven (months)†	3.7 (1.0-33.2)
Clad/LDAC-based regimen received for frontline HMA/ven subgroup (n=21)	
Clad/LDAC	10 (48)
Clad/LDAC/ATRA	1 (5)
Clad/LDAC/glasdegib	2 (10)
Clad/LDAC/venetoclax	8 (38)
Efficacy of clad/LDAC-based salvage for frontline HMA/ven subgroup (n=21)	
Evaluable for response	19 (90)
Overall response (CR/CRi)	7 (37)
CR	3 (16)
CRi	4 (21)
No response	12 (63)
MRD (among responders)	
Negative	4 (57)
Positive	2 (29)
Unknown	1 (14)
PFS (months)†	1.4 (0.4-20.9)
OS (months)†	2.3 (0.4-21.8)

*Unless otherwise specified, results are reported as n (%); †median (range)

Figure 1