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POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Venetoclax + Cladribine + Low-Dose Cytarabine in Acute Myeloid Leukemia Relapsed or Refractory to Venetoclax + Hypomethylating Agent

Nickolas Steinauer, MDPhD[1], Kristen McCullough, PharmD[2], Aref Al-Kali, MD[2], Hassan Alkhateeb, MD[2], Kebede Begna, MD[2], Abhishek A Mangaonkar, MBBS[2], Antoine Saliba, MD[2], Mehrdad Hefazi, MD[2], Mark R. Litzow, MD[2], William J. Hogan, MD[2], Mithun V Shah, MDPhD[2], Animesh D. Pardanani, MBBS, PhD[2], Talha Badar, MD[3], Hemant S. Murthy, MD[4], James M. Foran, MD[5], Cecilia Y. Arana Yi, MD[6], Ayalew Tefferi, MD[2], Naseema Gangat, MBBS[2]

[1] Mayo Clinic, Rochester, MN
[2] Division of Hematology, Mayo Clinic, Rochester, MN
[3] Mayo Clinic, Jacksonville, FL
[4] Department of Hematology/Oncology, Mayo Clinic, Jacksonville, FL
[5] Hematology/Oncology, Mayo Clinic, Jacksonville, FL
[6] Hematology/Oncology, Mayo Clinic, Scottsdale, AZ

Background

Venetoclax (Ven) in combination with hypomethylating agent (HMA) is the standard treatment for newly diagnosed elderly/unfit patients with acute myeloid leukemia (AML). Treatment options for patients with relapsed/refractory (RR) disease following Ven-HMA are limited in the absence of targetable mutations. In a recent phase 2 study, the addition of Ven to cladribine (CDA) plus low-dose cytarabine (LDAC), in newly-diagnosed elderly/unfit AML, resulted in complete remission with (CR) or without (CRi) count recovery rate of 93% (*J Clin Oncol 20;40(33)*). In the current study, we share our experience with this regimen in patients relapsed or refractory to Ven-HMA, treated outside of clinical trials.

Methods

Under an institutional review board approved minimum risk protocol, the Mayo Clinic (MN, AZ, FL) database was searched to identify patients with AML who failed treatment with Ven-HMA and subsequently received at least one cycle of salvage therapy with Ven-CDA-LDAC: Ven 100-400 mg, dose adjusted, d1-21, CDA 5 mg/m ^{2} d1-5, LDAC 20 mg twice daily d1-10, outside of clinical trials. Cytogenetic and molecular studies were performed at the time of Ven-CDA-LDAC initiation in most cases, by conventional karyotype and next-generation sequencing, respectively. The 2022 European LeukemiaNet (ELN) criteria were applied to define risk and response. Survival was calculated from the time of Ven-CDA-LDAC treatment start to last follow-up or death.

Results

Patient characteristics

A total of 39 RR AML patients (median age 65 years, 67% male, 64% *de novo*), with prior exposure to Ven-HMA, received Ven-CDA-LDAC (median 1 cycle; range 1-5). Study patients had received one (*n*=16), two (*n*=14), three (*n*=5), four (*n*=2), five (*n*=1) or nine (*n*=1) prior therapies, including Ven-HMA. Nine (23%) patients had relapsed following allogeneic hematopoietic stem cell transplant (AHSCT). ELN cytogenetic risk included intermediate (46%, *n*=18), and adverse (54%, *n*=21). Mutations involved *TP53* in 9 patients (23%), *K/ NRAS* in 8 (21%), *RUNX1* in 7 (18%), *TET2* in 6 (15%), *ASXL1* in 5 (13%), and *STAG2* in 5 (13%).

Response and toxicity

Eleven (28%) patients achieved CR (*n*=2; 5%) or CRi (*n*=9; 23%); median time to response was 1 month and median response duration 3.4 months. In addition, 2 (5%) patients each experienced partial remission (PR) and bone marrow aplasia without fulfilling criteria for morphologic leukemia free state. Measurable residual disease (MRD) was negative by multiparametric flow cytometry in 2 of 7 (29%) informative CR/CRi cases. CR/CRi rates were higher in females (54% vs 15%; *p*=0.01), *de novo* vssecondary AML (40% vs 7%; *p*=0.02), and absence of adverse karyotype (50% vs 9%; *p*<0.01), *K/NRAS* (35% vs 0%, *p*=0.01), *ASXL1* (32% vs 0%, *p*=0.05), or *STAG2* mutations (32% vs 0%, *p*=0.05) (Table 1). Multivariable analysis confirmed superior response in *de novo* AML (p<0.01), absence of adverse karyotype, (p<0.01), and absence of *K/NRAS* mutations (p=0.02). CR/CRi rates were not significantly affected by relapsed vs refractory setting (*p*=0.95), number of prior therapies (*p*=0.51), prior AHSCT

(*p*=0.64), or *TP53* mutations (*p*=0.64) (Table 1). Treatment-emergent toxicities included infections (49%, *n*=19), comprising bacteremia (*n*=11), pneumonia (*n*=10), peri-rectal abscess (*n*=6), and laboratory evidence of tumor lysis syndrome (3%, *n*=1).

Survival

At a median follow-up of 3.9 months, from initiation of Ven-CDA-LDAC, 31 deaths (79%), 6 relapses (15%), and 7 AHSCT (18%; including 5 in CR/CRi, 1 in aplasia) were documented. Median survival following Ven-CDA-LDAC was 4.6 months, and superior in the presence vs absence of CR/CRi (8.1 vs 2.9 months; *p*=0.01), and in patients receiving AHSCT (10.5 vs 3.4 months; *p*=0.02). Absence of adverse karyotype was also associated with superior survival (6 vs 3.4 months; *p*=0.05). Multivariable analysis confirmed the favorable survival impact of CR/CRi (*p*=0.03) and AHSCT (*p*=0.05); survival impact was not apparent for secondary AML (*p*=0.29) or *K/NRAS* (*p*=0.70) or *TP53* (*p*=0.10) mutations.

Conclusions

The current study suggests transplant bridging value for Ven-CDA-LDAC in AML patients relapsed or refractory to Ven-HMA, especially in the absence of adverse karyotype or *K/NRAS* mutation. AHSCT and achievement of CR/CRi appear to be indispensable for favorable post-Ven-CDA-LDAC survival.

Disclosures Alkhateeb: *Mayo Clinic:* Current Employment. **Begna:** *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Immunogen:* Research Funding; *MEI Pharma:* Research Funding. **Shah:** *Astellas:* Research Funding; *AbbVie:* Research Funding; *MRKR Therapeutics:* Research Funding; *Celgene:* Research Funding. **Murthy:** *Jazz Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Senti Biosciences:* Membership on an entity's Board of Directors or advisory committees; *CRISPR Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *Bavarian Nordic:* Membership on an entity's Board of Directors or advisory committees. **Foran:** *CTI:* Membership on an entity's Board of Directors or advisory committees; *NCI:* Membership on an entity's Board of Directors or advisory committees; *BeiGene:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Actinium:* Research Funding; *Kura:* Research Funding; *Sellas:* Research Funding; *Roivant:* Research Funding; *Novartis:* Research Funding; *Celgene:* Research Funding; *Astellas:* Research Funding.

OffLabel Disclosure: Venetoclax + Cladribine + Low-Dose Cytarabine in Acute Myeloid Leukemia Relapsed or Refractory to Venetoclax + Hypomethylating Agent

Table 1. Clinical characteristics at time of treatment with Venetoclax in Combination with Cladribine, Plus low-dose Cytarabine, for 39 patients with acute myeloid leukemia, relapsed/refractory to venetoclax and hypomethylating agent (HMA) stratified by achievement of complete response (CR) or CR with incomplete count recovery (CRi).

Variables	All patients N= 39	Patients in CR/CRi N= 11	Patients not in CR/CRi N= 28	*P-value/ Multivariate P-value*
Age in years, median (range): Age > 60 years, *n* (%)	65 (22-78) 25 (64)	67 (44-78) 8 (32)	63 (22-77) 17 (68)	0.21 0.7
Male, *n* (%)	26 (67)	4 (15)	22 (85)	**0.01**/0.42
AML type, *n* (%): *De novo* Secondary or therapy-related	 25 (64) 14 (36)	 10 (40) 1 (7)	 15 (60) 13 (93)	 **0.02/<0.01**
Hemoglobin, g/dl, median (range)	8 (5.4-16.2)	8 (6.5-10.2)	7.9 (5.4-16.2)	0.88
Leukocyte count x 10^9/L, median (range)	1.9 (0.1-41.9)	2.2 (0.1- 21.5)	1.8 (0.1-41.9)	0.95
Platelet count x 10^9/L, median (range)	27 (4-553)	35 (9-553)	24 (4-479)	0.46
Circulating blasts %, median (range)	13 (0-94)	5 (0-92)	13 (0-94)	0.94
Bone marrow blasts %, median (range)	20 (5-90)	14 (5-88)	23 (5-90)	0.30
ELN 2022 cytogenetic risk stratification, n (%): Intermediate Adverse	 18 (46) 21 (54)	 9 (50) 2 (10)	 9 (50) 19 (90)	**<0.01/<0.01**
Mutations on NGS, *n* (%): *TP53* *K/NRAS* *RUNX1* *TET2* *ASXL1* *STAG2* *CEPBA* *SF3B1* *U2AF1* *NPM1* *IDH2* *DNMT3A* *SRSF2* *BCOR* *CSF3R* *WT1*	 9 (23) 8 (21) 7 (18) 6 (15) 5 (13) 5 (13) 3 (8) 3 (8) 3 (8) 2 (5) 2 (5) 2 (5) 2 (5) 2 (5) 2 (5) 2 (5)	 2 (22) 0 (0) 2 (29) 3 (50) 0 (0) 0 (0) 1 (33) 1 (33) 1 (33) 2 (100) 1 (50) 1 (50) 0 (0) 1 (50) 1 (50) 2 (100)	 7 (78) 8 (100) 5 (71) 3 (50) 5 (100) 5 (100) 2 (67) 2 (67) 17 (67) 0 (100) 1 (50) 1 (50) 2 (100) 1 (50) 1 (50) 0 (0)	 0.64 **0.01/0.02** 0.98 0.22 **0.05**/0.22 **0.05**/0.22 0.84 0.84 0.84 **0.02**/0.47 0.50 0.50 0.24 0.50 0.50 **0.02**/0.47
Number of prior therapies, median (range)	2 (1-9)	2 (1-9)	2 (1-5)	0.51
Prior Allogeneic transplant, *n* (%)	9 (23)	2 (18)	7 (25)	0.64
Allogeneic transplant, *n* (%)	7 (18)	5 (45)	2 (7)	**<0.01**

Figure 1

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