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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Venetoclax and Azacytidine Treatment for High Risk Myelodysplastic Syndromes and Chronic Myelomonocytic Leukemia As a Bridge Therapy to Transplant. a GESMD Study

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Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) is the only potentially curative treatment for myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). Most common approach to bridge higher-risk MDS to alloHCT is to reduce tumor burden before alloHCT with azacytidine (AZA). Currently with this strategy less than 50% of patients achieve overall response rate (ORR) and less than 20% complete response (CR). Moreover, it is associated with a considerable rate of drop outs (approximately 50%) due to progression disease and mortality prior to alloHCT. Therefore, we need more effective treatments with faster and higher responses to facilitate more patients to undergo alloHCT. Venetoclax with AZA (VEN/AZA) is being investigated mostly in unfit MDS patients, it has shown higher ORR and early responses. Recently, a study suggested promising activity in 13 high-risk MDS patients who received VEN/AZA and proceeded to alloHCT (Komrokji et al, BCJ, 2022). The objective of our study is to analyze the feasibility, toxicity, and efficacy of VEN/AZA treatment in MDS and CMML patients who are intended to undergo alloHCT.

Methods

This is a retrospective multicenter study that includes high-risk MDS and CMML patients treated with VEN/AZA who are intended to undergo alloHCT. The response rate was assessed according to the IWG 2006, IWG 2023, ELN 2022. Savona criteria were used in CMML.

Results

A total of 23 patients were included, with a median age of 61 years (41-74), including 19 MDS and 4 CMML patients. Eight patients received VEN/AZA in a relapsed/refractory (R/R) setting, while 15 in first line (1L). Most patients received a 14-day scheme of VEN (n=16). The administration of VEN/AZA and other characteristics are described in Table 1.

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Grade 3/4 cytopenias were frequent (83% neutropenia 65% thrombocytopenia, 59% anemia), 17% experienced febrile neutropenia and 17% required hospitalization. G-CSF was used in 44% of patients, antifungal prophylaxis in 43%, and cycle delays due to cytopenias happened in half of them (47%). Thirty-day mortality was 0%, and one patient (4%) died within the first 60 days due to disease progression. The response rate following IWG 2023 criteria was: 7 CR (30%), 6 CR with limited count recovery (CR_L, 26%), 4 CR with partial hematologic recovery (CRh, 17%), 3 partial remissions (PR, 13%), 1 hematologic improvement (HI, 4%), and 2 no response (9%). The ORR was 91.3% (21/23), and the rate of composite complete responses (CRc) including CR, CR_L and CRh was 73.9% (17/23) . These responses occurred rapidly, all patients achieved the first response in 1 cycle and the median to best response was 1 cycle (range 1-3). In R/R patients the ORR was 87% and the CRc was 62%. Using the ELN 2022 versus IWG 2023 response criteria results in similar CRc, higher rate of CR (34% vs 22%) and lower ORR (86 vs 91%).
The median follow-up since the start of treatment was 13.6 months (95% CI: 5.2-21). The 2-year overall survival (OS) was 63% (95% CI ± 24%). Currently, there are 2 patients awaiting alloHCT. Among the 21 evaluable patients, 19 underwent alloHCT, resulting in a alloHCT rate of 91%. The 2 patients who were not transplanted included one CMML patient with disease progression prior alloHCT and one refractory MDS. AlloHCT was performed with a median of 3 prior cycles (range: 1-9), and the median time from the start of VEN/AZA to transplantation was 4 months (range: 2.5-10). One patient who did not respond to VEN/AZA was treated with chemotherapy prior alloHCT achieving CR. Two patients progressed before alloHCT, one achieved CR after chemotherapy and the other one has received a sequential alloSCT. The two-year post-transplant OS was 67% (95% CI ± 28%) (Figure 1). Four patients relapsed after alloHCT, resulting in a two-year cumulative incidence of relapse (CIR) of 37% (95% CI ± 28%). One of these patients was treated with VEN/AZA post-transplant and he is currently in CR for 1.5 years. 2-year transplant-related mortality was 6% (95% CI ± 12%).

Conclusion

Treatment with VEN/AZA as a bridge to alloHCT in MDS and CMML patients is feasible with a high rate of patients undergoing alloHCT. It provides high and quick responses, even in R/R patients, with low treatment-related toxicity.

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Table 1. Clinical, molecular and treatment characteristics of the cohort

Characteristics	n=23
Age at diagnosis, years, median (range)	61 (41-74)
Sex (male), n (%)	18 (78.3)
Leukocytes, x10^9/L, median (range)	2.54 (0.9-43.7)
Neutrophils, x10^9/L, median (range)	1.1 (0.17-7.9)
Monocytes, x10^9/L, median (range)	0.2 (0.05-4.19)
Platelets, x10^9/L, median (range)	58 (11-298)
Hemoglobin, g/L, median (range)	80 (60-136)
% Blasts in bone marrow, median (range)	10 (4-19)
Cytogenetic risk in MDS, n (%)	n=17
Very good	0
Good	6 (35)
Intermediate	1 (6)
Poor	6 (35)
Very poor	4 (24)
Cytogenetic risk in CMML, n (%)	n=4
Low	3 (75)
Intermediate	1 (25)
High	0
Treatment-related, *n (%)*	3 (13)
CMML FAB Classification, n (%)	n=4
Myelodysplastic	1 (25)
Myeloproliferative	3 (75)
MDS *2017 WHO Classification, n (%)*	n=19
MDS-EB1	6 (32)
MDS-EB2	11 (58)
MDS-MLD	1 (5)
MDS-RS-MLD	1 (5)
MDS *2022 WHO Classification, n (%)*	n=19
MDS-IB1	5 (26)
MDS-IB2	11 (58)
MDS-bi*TP53*	2 (10)
MDS-*SF3B1*	1 (6)
MDS *2022 ICC Classification, n (%)*	n=19
MDS/AML with myelodysplasia related mutations	10 (53)
MDS-EB	5 (27)
MDS-NOS	1(5)
MDS-*TP53*mut	2 (10)
MDS-*SF3B1*	1 (5)
2022WHO /ICC Classification, n (%)	n=4
CMML -1	1 (25)
CMML -2	3 (75)
R-IPSS, n (%)	n=17
Intermediate	1 (6)
High	9 (53)
Very high	7 (41)
IPSS-Mol, n (%)	n=16
Intermediate-low	1 (6)
Intermediate-high	2 (13)
High	7 (44)
Very High	6 (37)
CPSS, n (%)	n=4
Intermediate-2	4 (100)
High	0
CPSS-Mol high, n (%)	4 (100)

Mutations, n (%)	n=23
ASXL1	5
TP53	5
TET2	6
RUNX1	4
EZH2	3
GATA2	3
DNMT3A	3
PTPN11	2
BCOR	2
PHF6	2
CBL	2
SRSF2	1
NRAS	2
STAG2	2
ETV6	2
ZRSR2	2
U2AF1	2
IDH2	2
CSF3R	1
SH2B3	1
CEBPA	1
JAK2	1
MPL	1
SETBP1	1
BRAF	1
Transfusion dependence (%) (n=22)	9 (41)
First line, n (%)	15 (65)
Refractory/ relapse, n (%)	8 (35)
Allogeneic transplant, n (%) (n=21)	19 (83)
Donor type, n (%)	
HLA-identical family donor	4 (21)
Haploidentical family donor	2 (11)
Unrelated donor	13 (68)
HLA-identical (8/8)	5(38)
HLA-mismatched (7/8)	8(62)
Conditioning type, n (%)	n=19
Myeloablative	8 (42)
Reduced intensity	9 (47)
Sequential	2 (11)
Prophylaxis of Graft-versus-Host Disease (GVHD), n (%)	n=19
Cyclophosphamide + Tacrolimus	7 (37)
Cyclophosphamide + Tacrolimus + Mycophenolate	6 (32)
Cyclophosphamide + Tacrolimus + Sirolimus	1 (5)
Tacrolimus + Methotrexate	1 (5)
Tacrolimus + Mycophenolate	1 (5)
Tacrolimus + Rapamycin	1 (5)
T-cell depletion ex vivo	2 (11)
VEN/AZA treatment	
Type of hypomethylating agent, n (%)	
Decitabine	3 (13%)
Azacytidine	20 (87%)
Duration of Venetoclax, median (range)	14 (14-28)
Use of G-CSF, n (%) (n=18)	8 (44)
Use of antifungal prophylaxis, n (%)	10 (43)
Neutropenia, n (%)	19 (83)
Thrombocytopenia n (%)	15 (65)
Anemia n (%)	13 (59)
Neutropenic fever, n (%)	4 (17)
Fungal infection, n (%)	0
Admission, n (%)	4 (17)
Delay of the next cycle n (%) (n=19)	9 (47)
Days of delay of the next cycle, median (range)	13 (4-60)
Treatment modality, n (%)	
Ambulatory	18 (78)
Home care follow-up	11 (61)
Inpatient ramp-up	5 (22)

Figure 1. Swimmer plot of all patients. Combination HMA and Venetoclax was started at t=0. Circles represent the time and result of better response achievement. Allogeneic stem cell transplant and relapsed disease timepoints are indicated by squares and triangles respectively

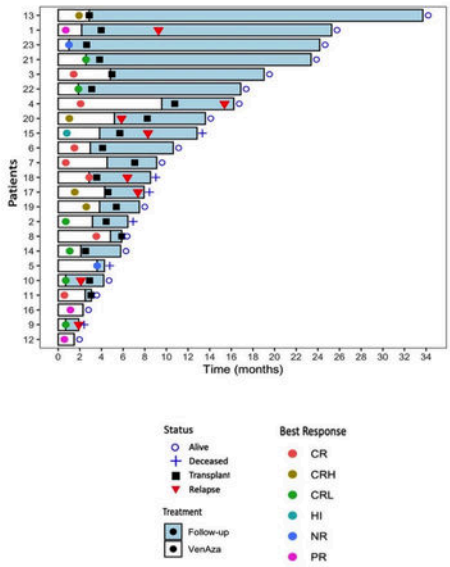

Figure 1

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