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ELEVENTH ANNUAL MEETING

VENETOCLAX IN COMBINATION WITH HYPOMETHYLATING AGENTS OR LOW-DOSE CYTARABINE FOR RELAPSED/REFRACTORY NPM1-MUTATED ACUTE MYELOID LEUKEMIA: CLINICAL EXPERIENCE FROM A REAL-LIFE SETTING

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BACKGROUND

NPM1^{mut} AML displays heterogeneous presentation and course, including patients with an excellent chemosensitivity and rapid clearance of measurable residual disease with long-term survival and others experiencing early relapse or even primary refractoriness. While first-line treatment of NPM1mut AML is well established[1], the optimal management of relapsed/refractory disease is still a matter of debate and outcomes remain unsatisfactory.

AIM

We performed a retrospective analysis on the clinical outcomes and molecular features of 17 adult patients treated with VEN+HMA or VEN+LDAC for R/R (including MRD failure) NPM1mut AML at our Institution between July 2018 and February 2022.

RESULTS

- Overall composite CR rate (CCR) was 59% (n=10/17)
- 60% MRD negative by RT-qPCR
- All CR occurred no later than cycle 2
- FLT3-ITD was strongly associated with treatment failure (CR rate 16%, p=0.021)
- 2/3 pts treated for MRD persistence/reappearance achieved MRD clearance
- 4/10 complete responders relapsed
- Median EFS: 11.8 months
- Median OS : 11.9 months

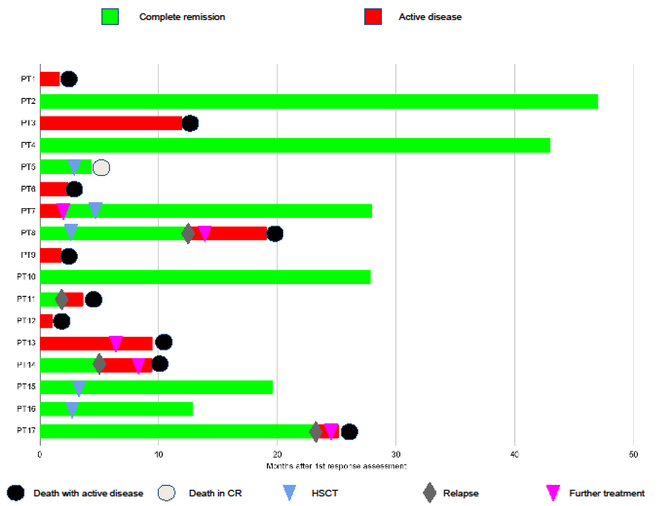
CONCLUSIONS

Although limited by the small sample size, our experience is confirmatory of the anti-leukemic activity and overall clinical safety of VEN in combination with HMAs or LDAC in R/R NPM1^{mut} AML patients not harboring FLT3-ITD mutations. The excellent efficacy and safety profile when used as MRD-directed treatment warrants further exploration of VEN-based lower intensity regimens in this clinical scenario.

RESULTS - 2

- Among patients achieving MRD negativity (N=6) only 1 relapsed
- Nine patients wee treated with an intention-to-transplant and 5/9 were able to proceed to HSCT in CR
- Long-term survival with ongoing CR exceeding 2 years was noted in a small number of patients not receiving allogeneic HSCT consolidation due to age or comorbidities
- Toxicity profile was overall manageable
- Patients treated for MRD positivity exhibited better overall hematological tolerance with fewer cytopenias

Patient	Age	Status	CR1 duration	Cytogenetic/molecular data (VAF)	Partner drug	Outcome
01	43	Early 2nd relapse after HSCT	5 months	46XY, DNMT3A R882H (8%), FLT3-ITD (AR 72.5%)	None	Refractory
02	71	1st Relapse	13 months	46XX, FLT3 D835Y (22%),	LDAC	MRD neg CR. Alive at 47 months,currently on single-agent VEN maintenance
03	70	2nd Relapse	3 months	46XX, SF3B1 E592K (46%), PTPN11 G60V (21%), FLT3 D835H (17%), NRAS G12D (4%)	LDAC	Refractory
04	67	1st Relapse	4 months	46XY, IDH1 R132C (NA)	LDAC	MRD neg CR; alive at 43 months; off treatment
05	38	1st Relapse	11 months	46XY, SRSF2 P95H (33%)	AZA	MRD pos CR, bridged to HSCT; death due to HSCT-related event
06	30	1st Relapse	2 months	+9q, FLT3 ITD positive (AR 13%), DNMT3A R882H (49%)	AZA	Refractory
07	33	1st Relapse	8 months	46 XY, NRAS G12V (47%)	AZA	Refractory; received further intensive chemotherapy, achieved MRD neg CR and was bridged to HSCT; alive in CR.
08	49	Molecular relapse	11 months	46XY, DNMT3A R882C (NA), TET2 S842X (NA), TP53 R175H (NA)	AZA	MRD pos CR, bridged to HSCT; subsequently relapsed and refractory to further reinduction attempts
09	36	Primary refractory	-	46 XY, DNMT3A c.1429+1G>AG (50%), SH2B3 p.L476F (48%), FLT3-ITD (AR 19%)	AZA	Refractory
10	65	1st Relapse	6 months	46XX, IDH2 R140Q (49%), NRAS G13D (46%), IDH1 R132Q (6%)	AZA	MRD neg CR; alive at 28 months; currently receiving dose-adjusted AZA/VEN
11	71	1st Relapse	5 months	46 XY, IDH2 R140Q (38%), SRSF2 P95A (36%), CBL C396 (7%), MPL Y591D (7%)	LDAC	MRD pos CR; subsequently relapsed and died due to disease progression
12	69	1st Relapse	4 months	46XY, CSF3R E835K (47%), DNMT3A R882H (35%)	AZA	Refractory
13	49	1st relapse	<2 months	46XY, FLT3 ITD (AR 60%), DNMT3A R882C (45%), IDH1 R132H (3%)	AZA	Refractory
14	66	1st Relapse	4 months	46XX, FLT3-ITD positive (AR 95%), DNMT3A G685R (16%), IDH2 R140Q (7%), U2AF1 Q157R (6%)	LDAC	MRD pos CR; subsequently relapsed and failed further treatment with gilteritinib
15	40	Molecular relapse	13 months	46XX, DNMT3A R882H (NA)	AZA	MRD clearance; bridged to HSCT; alive in CR
16	36	Molecular relapse	19 months	46XY, R132C (47%), PTPN11 S502L (26%)	AZA	MRD clearance;. bridged to HSCT; alive in CR
17	69	1st Relapse	11 months	46XY, PHF6 R274X (38%), DNMT3A Y735C (30%), NRAS G12D (29%), ASXL1 G646WfsX12 (NA),	DAC	MRD neg CR. Relapsed after 17 cycles; refractory to further reinduction attempts



REFERENCES

1. Falini B, Brunetti L, Martelli MP. How I diagnose and treat NPM1-mutated AML. Blood. 2021;137(5):589-599.

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