Low-dose Weekly Decitabine and Venetoclax in TP53-mutated Myeloid Malignancies

Lauren Shapiro MD[1], Ioannis Mantzaris MD[1], Aditi Shastri MD[1], Alejandro Sica MD[1], Nishi Shah MD[1], Noah Kornblum MD[1], Kira Gritsman MD[1], Eric Feldman MD[1], Amit Verma MD[1], Ira Braunschweig MD[1], Yogen Saunthararajah MD[2], Mendel Goldfinger MD[1]

[1]Montefiore, Bronx, NY, USA. [2]Cleveland Clinic, Cleveland, OH, USA

EINSTEIN Montefiore Einstein Cancer Center
Albert Einstein College of Medicine

Cleveland Clinic

Background

TP53-mutated (TP53^{mut}) AML and high-risk MDS are often treated with hypomethylating agents (HMAs) combined with venetoclax (Ven). However, myelosuppression often leads to dose-reductions and/or cycle delays. Administration of noncytotoxic doses of decitabine (Dec) 1×/week decreases HMA-mediated myelosuppression while maintaining S-phase–dependent DNMT1-targeting.[1]

In pre-clinical studies, single-dose Ven given prior to HMA administration inhibited de novo pyrimidine synthesis,[2] countering a major mechanism of resistance to HMAs without suppressing normal myelopoiesis.

Methods

We conducted a retrospective analysis of patients with TP53^{mut} MDS/AML at our institution treated with once weekly low dose dacogen and once weekly dose of venetoclax

Once weekly Regimen (q28 day cycle):

- Venetoclax PO, 400 mg on days 1, 8, 15, 22

- Decitabine SQ, 0.2 mg/kg (~5 mg/m^2) on days 2, 9, 16, 23

Patient Characteristics

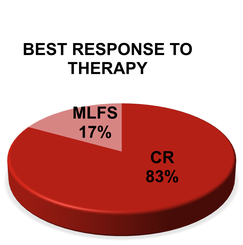
Table 1: Baseline Characteristics

Age/Sex	Ethnicity	ECOG	Comorbidities	2016 WHO Classification	Risk Category (R-IPSS or 2017 ELN)	Transfusion Dependent	Pre-treatment Blasts (%)	Time to initiation therapy (days)
54M	Caucasian	1	None	MDS-EB1 (de novo)	8	Yes	10	59
82M	Caucasian	2	HTN, HLD, COPD, CAD, GERD, BPH	AML with monocytic differentiation (s-AML)	Adverse	No	30	13
79F	Caucasian	2	COPD, CKD, Hypothyroidism, Sjogrens, SIADH, Hx SCLC	AML, NOS (de novo)	Adverse	Yes	23	7
79M	Caucasian	1	Hx stage IV DLBCL	MDS-EB2 (t-MDS)	8	Yes	3.52	3
39F	Black	2	HIV	AML with myelodysplasia-related changes (s-AML)	Adverse	Yes	22	7
82F	Hispanic	2	HTN, HLD, CKD	AML, NOS (de novo)	Adverse	Yes	90	4

Table 2: Baseline Cytogenetics and Molecular Mutations

Age/Sex	Diagnosis	Cytogenetics	FISH	Next-Generation Sequencing	TP53 Allele frequency (%)
54M	MDS	Complex	TP53, Monosomy 5, EGR1 deletion, ETV6, del13q14	TP53	34
82M	AML	Complex	del5q, +5p, RUNX1T1/8q	TP53, FLT3 ITD	48
79F	AML	Complex	del5q, ETV6/12p deletion, Monosomy 7	TP53	73
79M	MDS	Complex	TP53 deletion, Loss 7q (D7S468 (7q31), EGR1 Deletion	TP53	79
39F	AML	Complex	del5q, del13q, del18, +11, 11q anomalies	TP53, WT1, IDH1, JAK1, HIST1H1E	28
82F	AML	Complex	del5q, RUXN1, KMT2A (MLL) (11q23) amplification, EGR1 deletion	TP53, TET2	45

Results



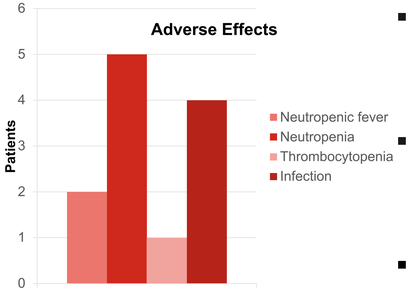
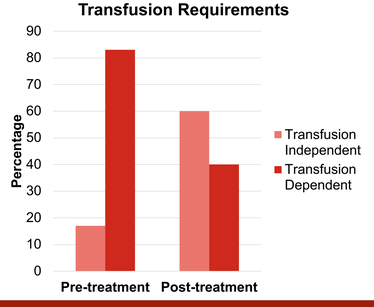
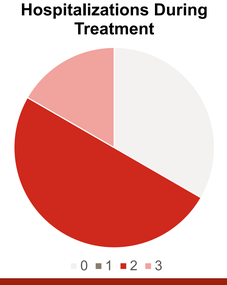


Table 3: Outcomes

Patient	Diagnosis	Line of Therapy	Best Response to therapy	Time to best response (months)	Duration of Treatment (months)	Reason for treatment discontinuation	Reduction of TP53 allele frequency (%)	Survival (mo)
1	MDS	1st line	CR	2.1	3.3	AlloSCT	100	11.4
2	AML	1st line	CR	9.4	19.1	Relapse	38	20.6
3	AML	1st line	CR	4.7	10.8	Relapse	83	11.8
4	MDS	1st line	CR	2.9	7.8	Relapse	Unk	9.4
5	AML	Primary refractory to Aza/Ven & Vyxeos	MLFS	1.7	2.4	Lost to follow-up	100	3
6	AML	1st line	CR	1.7	6.5	Death	46	6.5
			ORR 100%	Median 2.5 mo	Median 8.3 mo		Median 83%	Median 10.4 mo





Conclusion/Discussion

- Once weekly Ven with low-dose subQ Decitabine is well tolerated, yielding high response rates in TP53^{mut} MDS/AML.
- We demonstrate proof-of-activity for cytotoxic DNMT1-targeting to a high-risk, chemorefractory population by allowing sustained drug exposure.
- A low dose of once weekly decitabine/venetoclax may increase HMA/Ven efficacy independent of P53 and decrease myelosuppression/toxicity seen with standard HMA/ven dosing.
- A prospective clinical trial evaluating this weekly low dose regimen is actively enrolling patients with MDS and AML (NCT05184842).

References

1. Saunthararajah Y, Sekeres M, Advani A, et al. Evaluation of noncytotoxic DNMT1-depleting therapy in patients with myelodysplastic syndromes. *J Clin Invest*. Mar 2 2015.
2. Gu XT, R. Goldfinger, M et al. Venetoclax Inhibition of Pyrimidine Synthesis Guides Methods for Integration with Decitabine or 5-Azacytidine That Are Non-Myelosuppressive. *ASH meeting poster* 2020.