Real-world Experience with Decitabine Administered by a Non-cytotoxic, DNMT1-depleteting Regimen in Patients with Myelodysplastic Syndromes

Hassan Awada¹, Reda Mahfouz¹, Teodora Kuzmanovic¹, Bhumika Patel¹, Cassandra M. Hirsch¹, Tomas Radivoyevitch², Jaroslaw P. Maciejewski¹ and Yogen Saunthararajah¹.

¹Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio, USA; ² Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio, USA.

Background

Decitabine, at low concentrations, depletes DNA methyltransferase 1 (DNMT1). DNMT1-depletion triggers p53-independent terminal-differentiation of self-replicating malignant myeloid cells while sparing normal dividing cells. High decitabine concentrations, however, have off-target anti-metabolite effects and are cytotoxic to normal dividing cells, a problem since these cells are needed to reverse the low blood counts that cause morbidity and death.

Objective

To determine clinical safety and benefits of decitabine administered by a dose, schedule and route of administration designed to minimize cytotoxicity and maximize DNMT1-depletion.

Materials & Methods

Single-arm, open-label phase 1/2 study followed by off-label use in patients if indicated for risk/benefit (clinical) reasons. Patients were treated at Cleveland Clinic Taussig Cancer Institute. All patients were followed from diagnosis till death or loss-to-follow-up. Patients received reduced decitabine dosages (0.1–0.2 mg/kg/day compared with the FDA-approved 20–45 mg/m²/day dosage, a 75%–90% reduction) to avoid cytotoxicity. These well-tolerated doses were frequently administered 1–2 days per week, instead of pulse cycled for 5 days every 4 weeks, to increase the fraction of malignant cells potentially subject to S-phase dependent DNMT1-depletion.

Clinical Parameter	Responders n (%)	Non-responders n (%)	P value
Age (yr) (median/range)	69 (52-90)	68 (45-85)	0.1
Gender	22M (73%)/ 8F (27%)	27M (69%)/12F (31%)	0.79
Relapse/progression on 5-Aza or len	12 (40%)	24 (62%)	0.09
Previous cancer treated with chemotherapy or radiation	4 (13)	1 (3)	0.15
Pretreatment BM myeloblast % (range)	2 (0-80)	4 (1-64)	0.09
RAEB or CMML	10 (33%)	9 (23%)	0.41
Pretreatment ANC (x10 ⁹ /l) (median/range)	3.04 (0.24-32.34)	1.23 (0.01-52.2)	<0.0001
Pretreatment platelets (x10 ⁹ /l) (median/range)	34 (6-242)	76 (4-280)	0.09
Pretreatment reticulocytes (x10 ⁹ /l) (median/range)	54 (8-173)	46 (6-222)	0.03
Disease Genetics			
High-risk cytogenetics (chromosome 7 deletions and/ or ≥ 3 chromosomal abnormalities)	7 (25%)	8 (21%)	1
PRC2 mutation/deletions	4 (15%)	8 (24%)	0.5
TET2 system mutation	6 (23%)	2 (6%)	0.1
Pharmacodynamics and mechanisms of action			
Number of weeks on regimen (median/range)	82 (14-347)	26 (3-131)	<0.0001
Hematopoietic capacity			
Pretreatment BM Cellularity %	70 (10-95)	48 (5-100)	<0.0001

Results

69 patients with myeloid neoplasms (MDS 54%, MDS/MPN 14%, AML 15%, MPN 17%) were treated. The median patient age was 69 years (range, 45-90 years). 52% of the patients (n=36) had disease that relapsed/progressed on 5-azacytidine and/or lenalidomide; 7% (n=5) had received chemoradiation to treat other cancers. Anti-emetics were not needed. Blood count improvements meeting International Working Group (IWG) criteria for response occurred in 43% of subjects (n=30) and were highly durable (see figure). Complete remission occurred in 14% (n=10). Response rates were significantly higher in MDS subtype MDS/MPN (P=0.02). Kaplan-Meier method showed significantly better (p=0.02) median survival (months) in responders (31.03m) vs non-responders (17.74m). We previously reported correlates demonstrating a non-cytotoxic, differentiation-based mechanism-of-action (Saunthararajah et al, *JCI* 2015).

Conclusion

DNMT1-depletion is validated scientifically to terminate malignant but not normal self-replication, moreover, by a p53-independent pathway. Accordingly, a decitabine regimen designed (and confirmed by correlates) to deplete DNMT1 without cytotoxicity, was very well-tolerated and produced meaningful, durable benefit in patients with diverse myeloid malignancies.

References

Saunthararajah et al, *Journal of Clinical Investigation* 2015