Low dose decitabine + Ven in elderly AML patients

Raport preliminar

Introduction

Acute myeloid leukemia – (Cluj, Romania)

Median overall survival: 8.6 months

Hypomethylating agents: 10 months

Best supportive care: 3.4 months

AML-085

Real-World Treatment Patterns and Clinical Outcomes in Romanian Patients With AML Unfit for First-Line Intensive Chemotherapy

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bjh short report

Extended experience with a non-cytotoxic DNMT1-targeting regimen of decitabine to treat myeloid malignancies

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Summary

The nucleoside analogue decitabine can deplete the epigenetic regulator DNA methyltransferase 1 (DNMT1), an effect that occurs, and is saturated at, low concentrations/doses. A reason to pursue this molecular-targeted effect instead of the DNA damage/cytotoxicity produced with high concentrations/doses, is that non-cytotoxic DNMT1-depletion can cytoreduce even p53-null myeloid malignancies while sparing normal haematopoiesis. We thus identified minimum doses of decitabine (0·1–0·2 mg/kg) that deplete DNMT1 without off-target anti-metabolite effects/cytotoxicity, and then administered these well-tolerated doses frequently 1–2X/week to increase S-phase dependent DNMT1-depletion, and used a Myeloid Malignancy Registry to evaluate long-term outcomes in 69 patients treated this way. Consistent with the scientific rationale, treatment was well-tolerated and durable responses were produced (~40%) in genetically heterogeneous disease and the very elderly.

Keywords: myeloid neoplasms, decitabine, noncytotoxic DNMT1 depletion.

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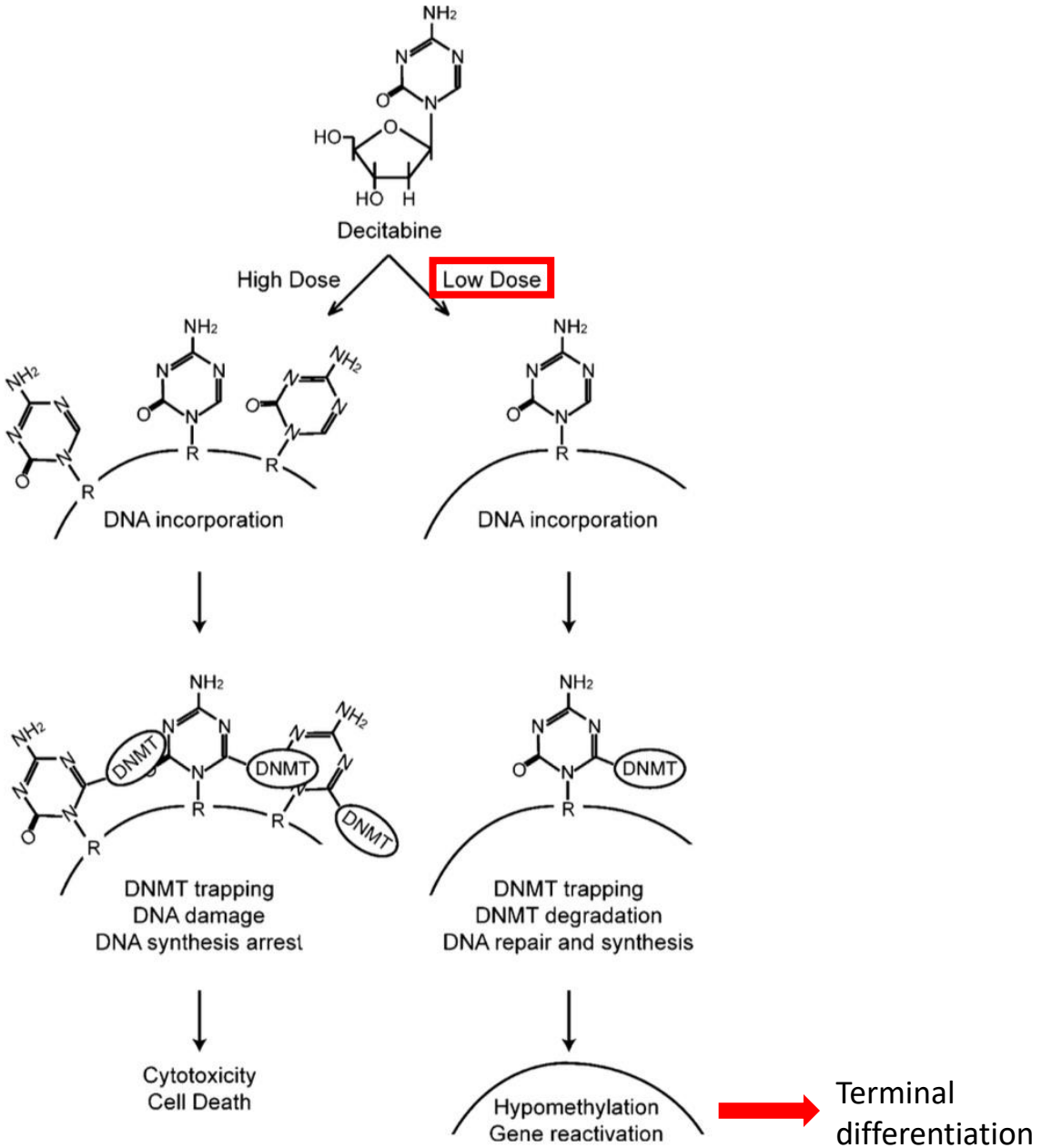
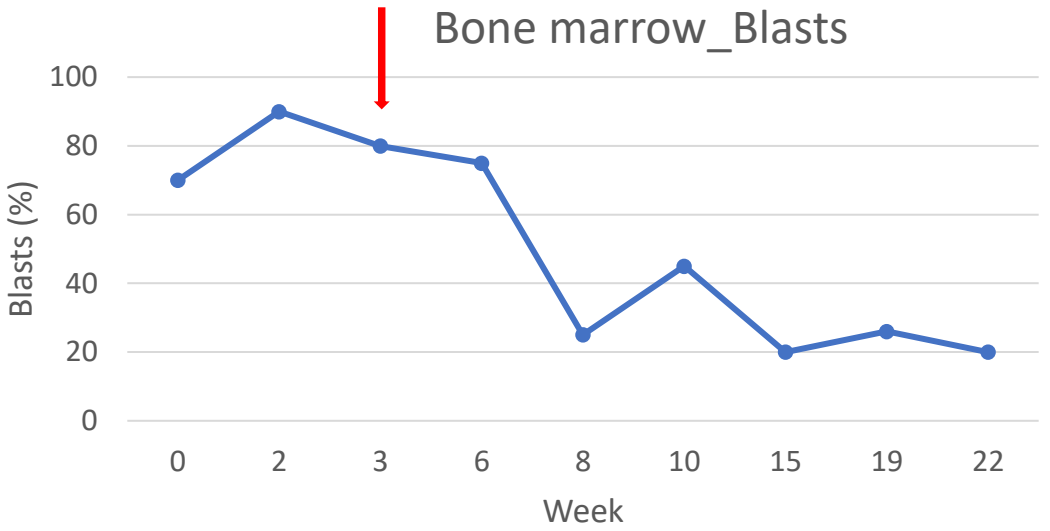
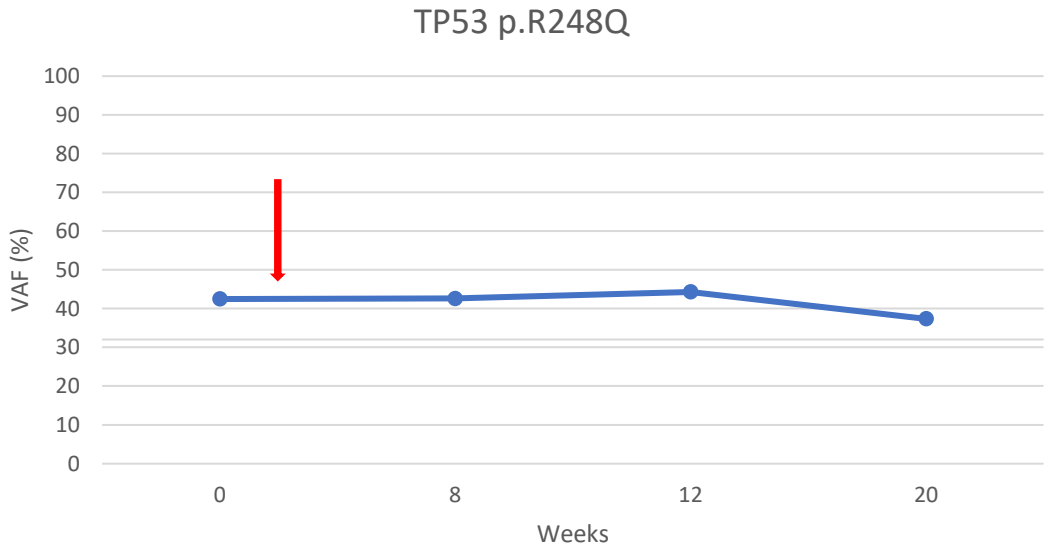


Y, Aoki E, Issa JPJ. Decitabine—Bedside to bench. Crit Rev Oncol Hematol. 2007 Feb;61(2):140–52.

Patient 1

Cytogenetics	at diagnosis
Karyotype	abnormal 45,X[1]/46,XX,t(7;14)(p21;q22)[1]/46,XX[18]
Molecular genetics	
FLT3 TKD	negative
FLT3 ITD	negative
NPM1	negative
Seq	
TP53 p.R248Q	present





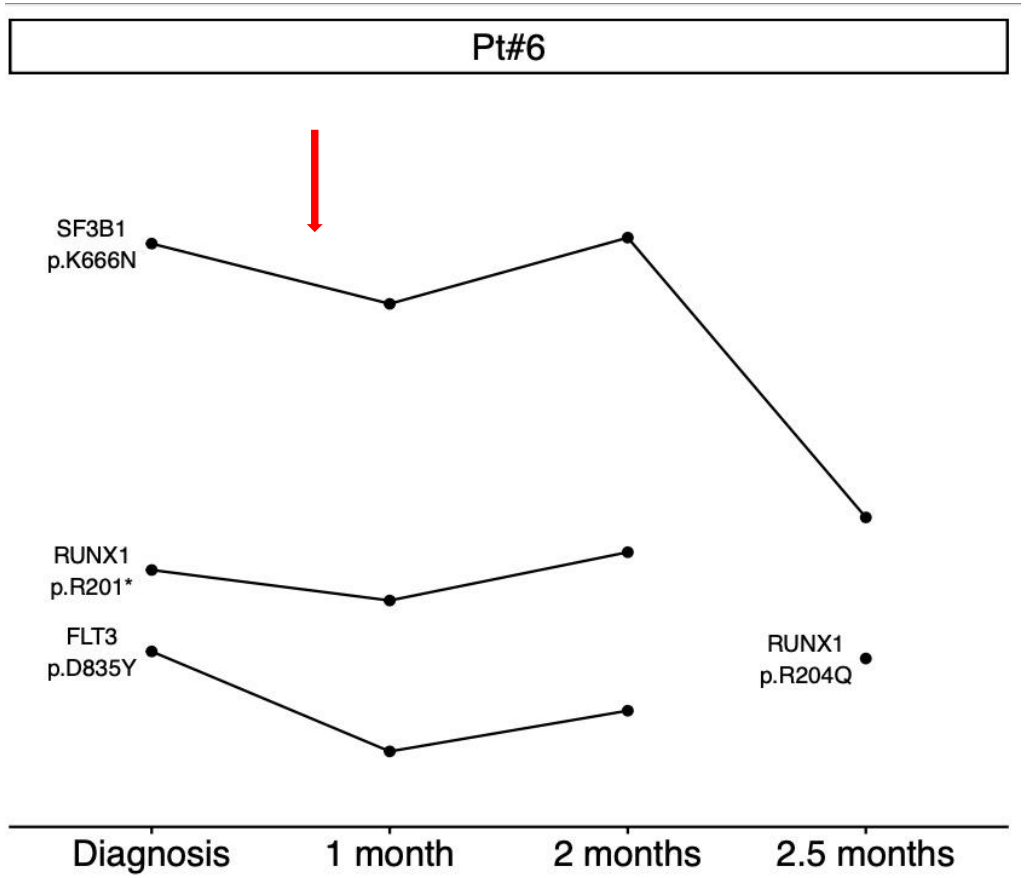
Patient 2

Cytogenetics	at diagnosis
Karyotype	normal

Molecular genetics	
FLT3 TKD	positive
FLT3 ITD	positive
NPM1	negative

Seq	
SF3B1 p.K666N	present
RUNX1 p.R201	present
FLT3 p.D835Y	present
RUNX1 p.R204Q	at 2,5 months

VAF (%)	diagnosis	1 months	2 months	2,5 months
SF3B1 p.K666N	80,26	71,46	81,13	40,24
RUNX1 p.R201*	32,55	28,09	35,15	
RUNX1 p.R204Q				19,61
FLT3 p.D835Y	20,64	6,03	11,98	



Patient 3

Cytogenetics	at diagnosis
Karyotype	negative
Molecular genetics	
FLT3 TKD	negative
FLT3 ITD	negative
NPM1	negative
Seq	
SRSF2 p.P95H	at diagnosis
NPM1 p.W288Cfs*12	at 5 months

Gene	Weeks	VAF (%)
SRSF2	0	40,21
SRSF2	8	42,22
SRSF2	20	10,68
NPM1	20	2,85