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MUTATIONAL ANALYSIS OF MDS AND AML OCCURRING AFTER TREATMENT FOR ACUTE PROMYELOCYTIC LEUKEMIA (APL) - A REPORT OF 9 CASES

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Background

- 1-2% of APL treated with ATRA-chemotherapy develop MDS/ AML (non APL), a problematic side effect for a highly curable disease

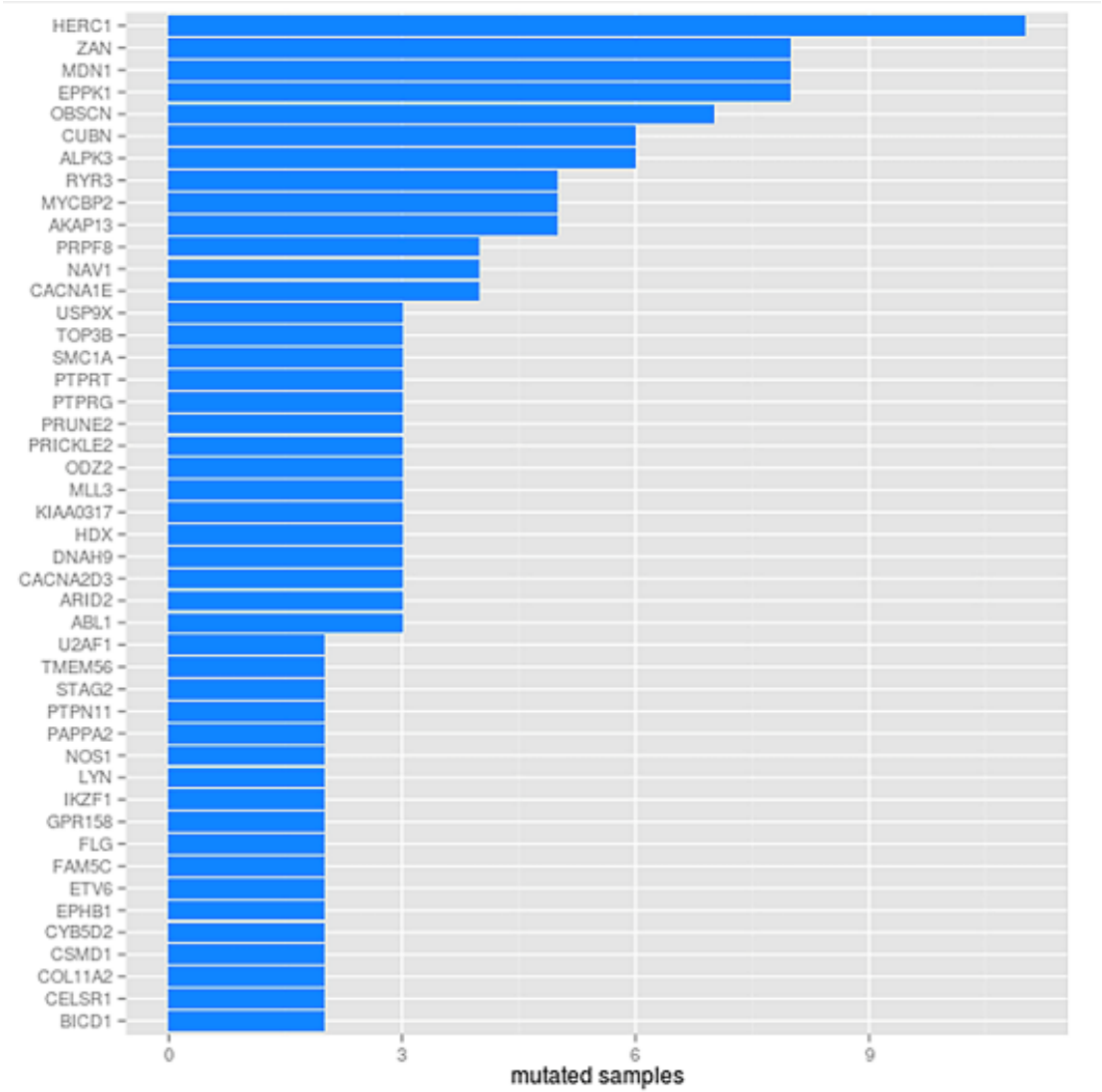
MDS with Complex Caryotype

Patient no.	*Sex/ age*	*WBC ($\times 10^9$ /l) at APL diagnosis*	*Karyotype at APL diagnosis*	*FAB type*	*PML-RARα at APL diagnosis*	*Karyotype at diagnosis of MDS*	*Progression to AML*	*Survival from MDS diagnosis (months)*
1	F/61	148	46, XX, del(3)(q24q26), del(5)(q23q32), t(7;11)(p11;p12), t(15;17)(q22;q21)	Classical APL	Positive	45, XX, del(5)(q21q34)-7	M0 AML after 6 months	11.5
2	F/56	0.8	46, XX, t(15;17)(q22;q21)	Classical APL	Positive	46, XX, del(5)(q22q34), t(15;21)(p11;q21), -17, +mar	No	25.4
3	M/52	0.7	46, XY, t(15;17)(q22;q21)	Classical APL	Positive	43, XY, del(5)(q12q35), add(11)(q23), dup(12) (q12q22), -17, -18, -22	M0 AML after 1 month	0.8
4	M/57	1.4	46, XY, del(9)(q21q31), t(15;17)(q22;q21)	Micro-granular variant APL	Positive	45, XY, -5, der(7)t(7;20) (q11;p? or q?), der(10)t(7;10;20) (q3?;q2?; p? or q?), -13, der(17)t(10;17)(q2?;p11), -20, del(20)(q11), +mar1, +mar3/ 47, idem, del (X) (q26), der(1) (1;?)(p36;?), +8, +mar2	No	24+
5	M/73	1.3	Failure	Classical APL	Positive	45, XY, -8, t(8;11)(q32;q21)	M0 AML after 18 months	7.5
6	M/54	0.9	46, XY, t(15;17)(q22;q21)	Classical APL	Positive	45, XY, t(3;17)(p11;q11), del(5)(q13q33), del(6)(p22),-17	No	4+

Lobe , Leukemia 2003

Mutational landscape in APL

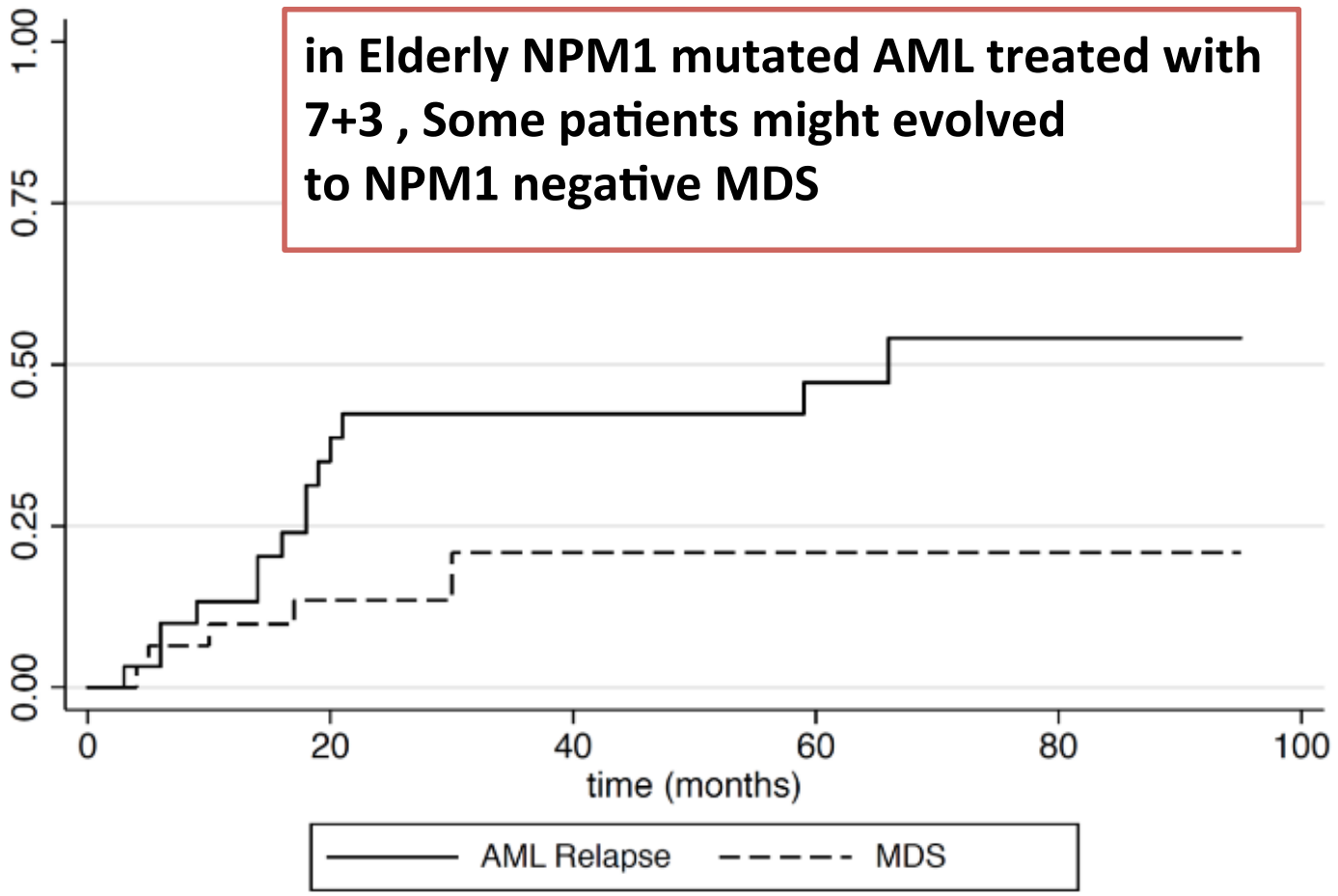
high number of somatic mutations affecting more many different genes (mainly in a non-recurrent manner), suggesting that APL is a heterogeneous disease with secondary relevant changes



Mariam Ibáñez , PLOS one 2016

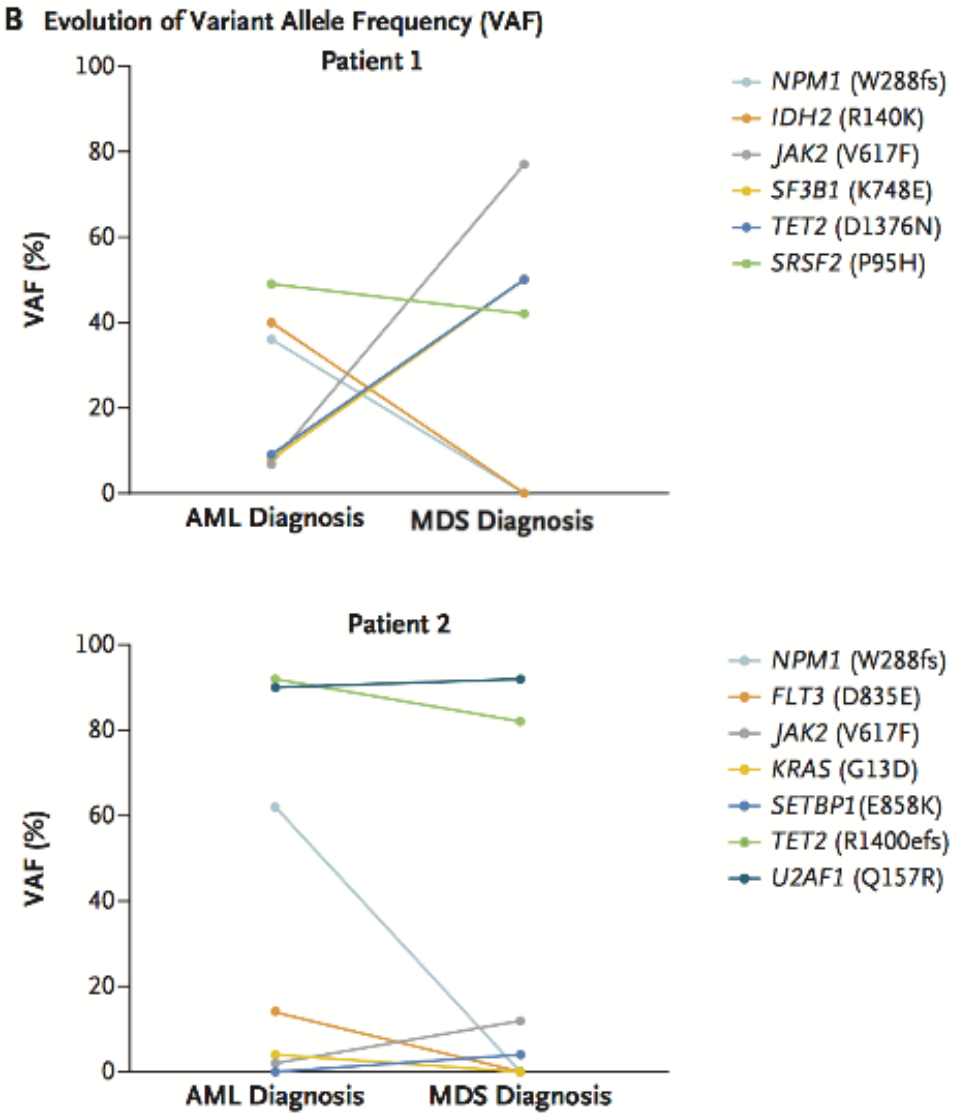
MDS following NPM1+ AML

in Elderly NPM1 mutated AML treated with 7+3 , Some patients might evolved to NPM1 negative MDS



Morin, N Engl J Med, 2016

MDS following NPM1+ AML



- WES at AML
- WES at MDS evolution
- All NPM1+ at AML
- All NPM1- at MDS
- others Somatic mutations present at the MDS phase were already present at AML diagnosis, suggesting an underlying MDS (with secondary acquisition of NPM1 mutation at the time of AML).

Morin, N Engl J Med, 2016

Hypothesis

- We wondered whether MDS/AML after APL were
  - t-MDS/AML
  - or underlying MDS with APL progression.

Methods

- 956 newly diagnosed APL treated with ATRA-CT (APL 2006 trial)
- 9(1%) developed MDS/AML in 1st CR.
- Paired marrow samples
  - at APL
  - and MDS/AML diagnosis were analyzed on genomic DNA for the 30 most frequently mutated genes in MDS/AML, by NGS.

Patients characteristics

UPN	APL risk	Interval to MDS/ AML (months)	WHO classification	Karyotype
1	High	33	RCMD	Del(5q), Add(12)p, del(17p)
2	High	30	RCMD	Complex with Del5q)
3	Int	24	RAEB-2	-7
4	Low	47	RARS	complex with -5 and -7
5	Low	24	RARS	Complex, with del(5q), del(6), Del(7q), Del17p),
6	Low	64	AML	-7, Del(5q)
7	High	35	RAEB-1	Normal
8	High	42	RAEB-2	-7, abn 13
9	High	36	RAEB-2	-7

Mutations at diagnosis of APL

UPN	APL risk	**Mutations frequency**
1	High	**None**
2	High	**DNMT3A, WT1, FLT3-ITD**
3	Int	**None**
4	Low	**PHF6**
5	Low	**None**
6	Low	**FLT3-ITD**
7	High	**FLT3-ITD**
8	High	**FLT3-ITD, FLT3-TKD**
9	High	**FLT3-TKD NRAS WT1**

At APL diagnosis, karyotype found only t(15 ;17), and mutations were mostly FLT3-ITD or FLT3-TKD

Mutations at diagnosis of MDS

At MDS/AML diagnosis,
Karyotype was typical of tMDS/ AML
and/or
patients had MDS type mutations.

WHO classification	Karyotype	**Mutations (Variant allele frequency)**
RCMD	Del(5q), Add(12)p, del(17p)	**None**
RCMD	Complex	**None**
RAEB-2	-7	**ASXL1, CBL RUNX1**
RARS	complex	**DNMT3A TP53**
RARS	Complex,	**TP53**
AML	-7, Del(5q)	**TP53 ASXL1**
RAEB-1	Normal	**TET2, SMC1A**
RAEB-2	-7, abn 13	**PTPN11**
RAEB-2	-7	**EZH2 KRAS GATA2**

Correlation between APL and MDS

APL	MDS
None	None
DNMT3A (45%) WT1 FLT3-ITD	None
None	ASXL1 CBL (10%) RUNX1 (9%)
PHF6 (15%)	DNMT3A (18%) TP53 (51%)
None	TP53 (36%)
FLT3-ITD	TP53 (13%),ASXL1
FLT3-ITD	TET2 (31%), SMC1A (43%)
FLT3-ITD FLT3-TKD (34%)	PTPN11 (43%)
FLT3-TKD (40%), NRAS (2%) WT1 (30%)	EZH2 (34%) KRAS (28%), GATA2 (9%)

None of the mutations identified at APL diagnosis was found at MDS/AML diagnosis, and vice versa, strongly suggesting that APL and MDS/ AML arose from distinct clones.

Conclusion

- No evidence of underlying MDS was found at APL diagnosis Cytogenetic and mutational profiles of those MDS/AML were suggestive of tMDS/AML.
- Thus, MDS/AML occurring during the course of APL treated with ATRA and CT have characteristics of therapy-related cases.

Acknowlegments

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