Progetto formativo SIE
Dall'emopoiesi clonale alle leucemie «therapy-related»
Bologna, 09 Aprile 2019

SPONTANEOUS JAK2 ALLELE BURDEN OSCILLATION OBSERVED IN A PATIENT WITH SECONDARY ACUTE LYMPHOBLASTIC LEUKEMIA ARISING IN THE CONTEXT OF JAK2 POSITIVE ESSENTIAL THROMBOCYTEMIA

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Integrata con il Servizio Sanitario Regionale

PROGETTO FORMATIVO SIE
DALL'EMOPOIESI CLONALE ALLE LEUCEMIE "THERAPY-RELATED"
Bologna, Starhotels Excelsior, 09 aprile 2019

DICHIARAZIONE

Relatore: GIULIA CAMPAGNA

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

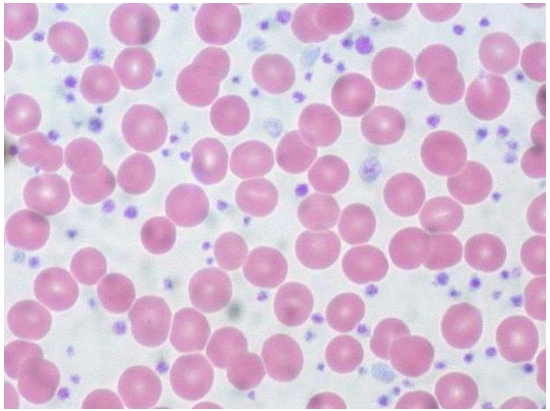
CLINICAL CASE

♀66 years old

- October 2012: thrombocytosis and leukocytosis

  Hb 14,8 g/dL ; PLT 580.000/mm^3; WBC 12.500/mm^3

  Absence of thrombotic events, headache or itching



JAK 2-V617F → **POSITIVE on PB**

BONE MARROW BIOPSY → **ESSENTIAL THROMBOCYTEMIA**

CLINICAL CASE

Table 2 The IPSET criteria for evaluating the thrombotic risk of essential thrombocythemia (ET)

Risk factor	HR	Score
Age > 60 years	1.50	1
Cardiovascular risk factors	1.56	1
Previous thrombosis	1.93	2
JAK2V617F	2.04	2

Low risk implies a score = 0–1; intermediate risk, score = 2; and high risk, score ≥ 3

Barbui T. et al Leukemia 1057–1069 (2018)

THERAPY

-ASA 100 mg/die

-Hydroxyurea 500-1000 mg/die

Good response:

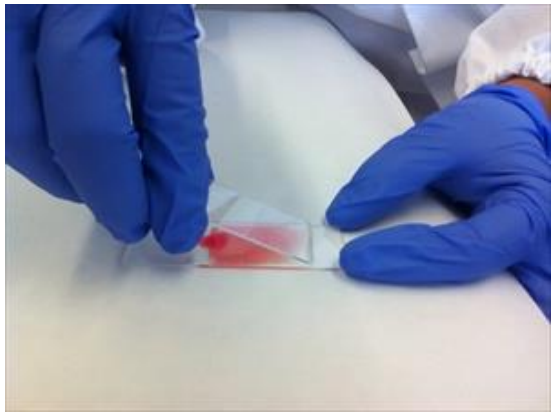
- Controlled platelet counts

- No thrombotic events

CLINICAL CASE

- Oct 2012- July 2018 : ndp
- August 2018: fever, fatigue, joint pain

Hb 10,4 g/dl WBC 20.680/mm^3 PLT 23.000/mm^3



PERIPHERAL BLOOD SMEAR → **lymphoid blast cells (80%)**

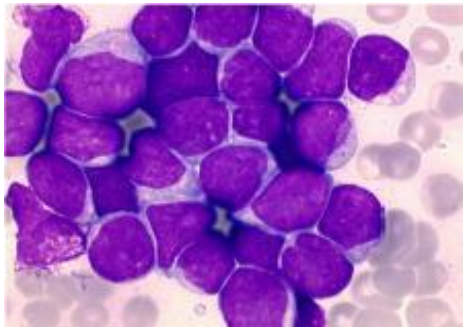
NEW DIAGNOSIS

BONE MARROW ASPIRATE: lymphoid blast cells (95%)

-IMMUNOPHENOTYPE: CD34- DR- cCD3+ CD7+ CD2+ CD1a+ CD8+ CD10+ MPO –

-CITOGENETIC TESTING: 46,XX [12] no abnormalities

-MOLECOLAR STUDIES: JAK2-V617F mutation **undetectable**.



T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA
(Cortical T-ALL)

MRD monitoring thanks to GIMEMA

IN LITERATURE…

Table 1. Summary of cases of MPN that transformed to ALL reported in the literature.

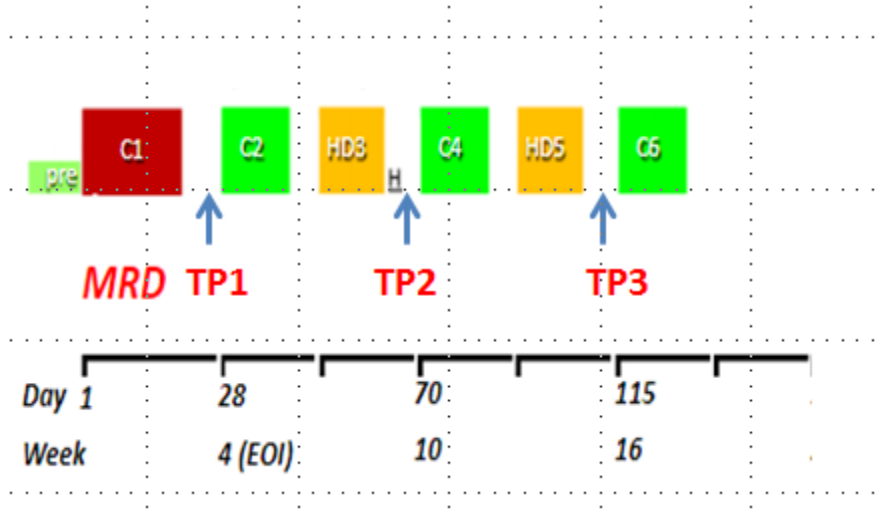
Case no.	Age/gender	MPN subtype	JAK2 status	Cytogenetics (of ALL)	Time to progression (years)	Phenotype	Clinical outcome	Reference
1	61/M	PMF	NR	Aneuploid	5	B cell	Died	[37]
2	58/F	PPV-MF	NR	NR	18	Burkitt's	Died	[37]
3	54/M	PPV-MF	Exon 12	Diploid	4	B cell	Died	[25]
4	63/M	PPV-MF	NR	NR	6	B cell	Died	[38]
5	53/M	PMF	NR	NR	2	B cell	Died	[39]
6	74/M	PPV-MF	NR	NR	6	Null	Died	[40]
7	42/M	PV	NR	Del 6q, +8	10	Null	Died	[41]
8	20/M	PV	NR	NR	10	T cell	Died	[41]
9	68/F	PV	NR	Complex	25	B cell	Died	[42]
10	76/M	PV	NR	Diploid	16	Common	Died	[43]
11	54/F	PV	NR	NR	13	Common	Alive	[44]
12	65/M	ET	V617F	Del 9p13	16	B cell	Unknown	[24]
13	59/M	PET-MF	V617F	Del 13q and 20q	10	B cell	Unknown	[24]
14	67/F	ET	V617F*	t(9;22)	16	B cell	Died	[26]
15	65/F	ET	Neg†	Hyperdiploid	3.5	B cell	Alive	[45]
16	70/F	ET	NR	Diploid	19	B cell	Unknown	[46]
17	56/M	PMF	Neg	t(9;22), del 20q	1	B cell	Died	[47]
18	65/F	PMF	V617F	Complex, monosomal	11	B cell	Died	Present case

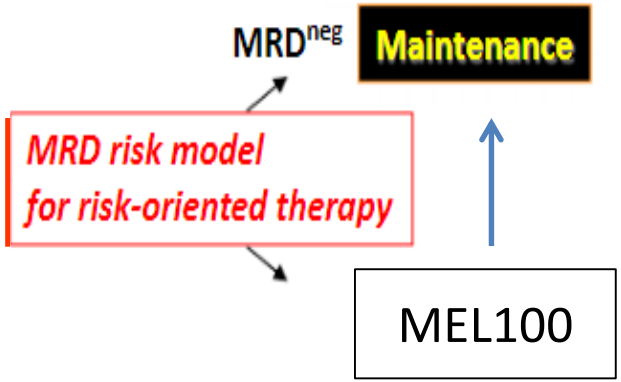
NR, not reported; PMF, primary myelofibrosis; PPV-MF, postpolycythemia vera myelofibrosis; PET-MF, postessential thrombocythemia myelofibrosis; ET, essential thrombocythemia.
*Not in the ALL clone at transformation.
†*CALR* mutant.

Alhuraiji et al Clin Case Rep. 2017 Dec 6;6(1)

Transformation of Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) into acute lymphoblastic leukemia remains an extremely **rare event,** normally associated with **poor prognosis**.

TREATMENT PLAN: NILG 10/07 age>65





- 6 vs 8 blocks
- Reduced Idarubicin
- Asparaginase: 1 dose
- GCSF

C3, C5 → Admitted for HD-MTX

C1, C2, C4, C6 → Outpatient clinic

Mol. Marker	DGN	TP1 – W4	TP2 - W10	TP3 – W16
Vγ I-Jγ1.1	**POS**	Neg. $<1 \times 10^{-4}$	Neg. $<1 \times 10^{-4}$	Neg. $<1 \times 10^{-4}$
JAK2V617F	**NEG**	20,4%	23,7%	29,9%

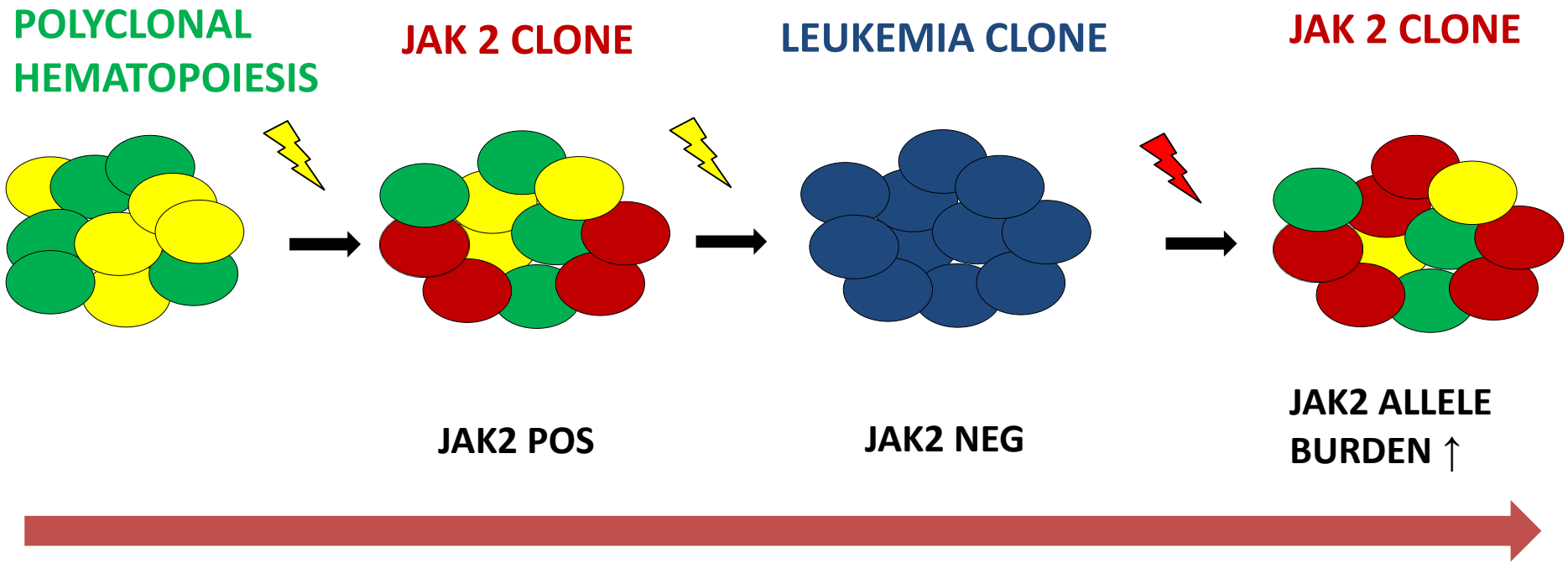
BM after cycle 1, 3 and 5 (Time point 1, 2 ,3) showed complete remission with MRD negativity.

After CR, JAK2-V617F detectable again, with increasing allele burden level.

PLATELET COUNTS

From diagnosis of ALL to maintenance

OUR HYPOTESIS – GAME OF CLONES



CONCLUSIONS

Two different clones competed for the same niche.

JAK 2 CLONE **VS** **LEUKEMIA CLONE**

JAK2V617F disappeared at leukemia diagnosis:
SUPPRESSIVE vs DILUITION EFFECT (?)

JAK2 clone reappeared when CR has been achieved:
PROLIFERATIVE ADVANTAGE UNDER CHT (?)

Grazie per l'attenzione!