

Clinical management of myeloid neoplasms with overlapping clinical and pathological features.

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Disclosures

None

Objectives:

- Increase awareness amongst health care providers about myeloid neoplasms which are difficult to categorize.
- Use a case based approach to highlight the critical role of integrating clinical presentation with pathological findings, cytogenetic data and molecular findings to formulate and optimize a management plan.

Case 1

70 year old lady, presented to UMC ER in 2015 for transfusion.

Five year history of “anemia” for which she received 60,000 units of erythropoietin every week. Two years prior to coming to UMC, she had become transfusion dependent requiring PRBC every 3-4 weeks. She estimated having received 25 units over 2 years.

Twelve year history of parkinsonism, progressing on levodopa/carbidopa. Over the years, she had been on multiple medications and supplements prescribed by her physicians in Mexico. She had stopped levodopa/carbidopa due to dyskinesia and was currently on pramipexole.

Physical exam:

Decreased facial expression, hypophonia, cogwheeling, rigidity and stooping narrow based gait. Bilateral resting tremor.

Conjunctival pallor

No adenopathy and no hepatosplenomegaly.

Labs:

Hb 6.9 gm/dl, MCV 94.4 fl

WBC 4500/mcl; PMN 50.2%, L 30.2%

Platelets: 547,000/mcl

Absolute reticulocyte count 70,000/mcl.

Iron saturation 88%

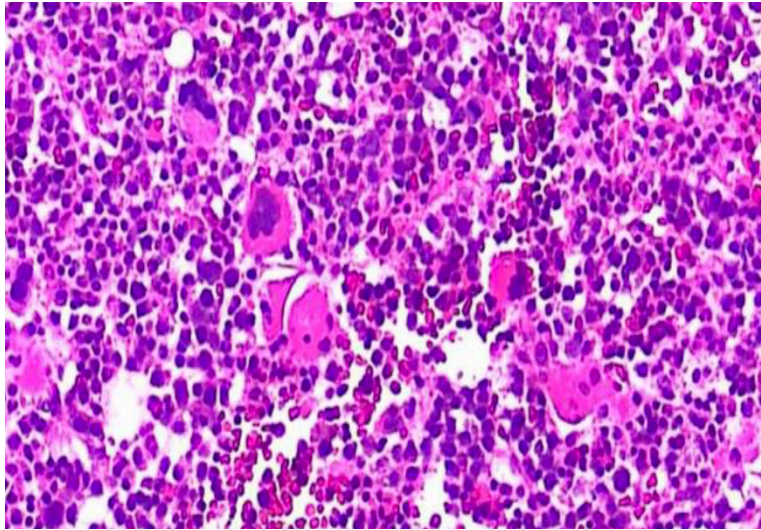
Ferritin: 1866ng/ml

B12: 561pg/ml

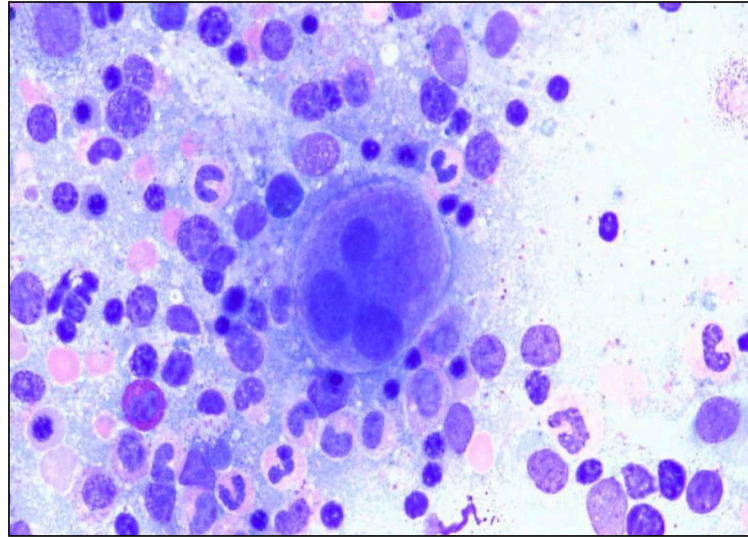
Folate: 9.5ng/ml

Erythropoitin level: 140.8mIU/ml (2.6-8.5)

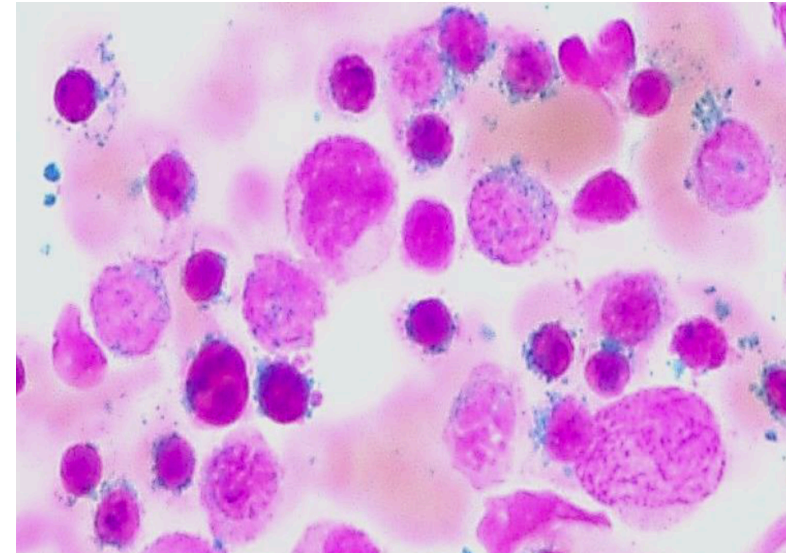
Bone marrow biopsy (Jan 2015)



Hypercellular marrow with ***proliferation*** of large atypical megakaryocytes.



High power view showing one of the megakaryocytes.



Erythroid ***dysplasia*** with Ring Sideroblasts (RS)

Blasts <5%, Karyotype: 46 XX

RS can be seen in both clonal(ie malignant) and non clonal conditions.

Clonal

- a) MDS-RS-SLD
- b) MDS-RS-MLD
- c) MDS-excess blasts-with ring sideroblasts
- d) MDS-U- with ring sideroblasts
- e) Essential thrombocytosis with RS
- f) Primary myelofibrosis with RS
- g) MDS/MPN with ring sideroblasts and thrombocytosis
- h) CMML with ring sideroblasts
- i) MDS/MPN-U with ring sideroblasts

Non-clonal

- a) Hereditary sideroblastic anemias
- b) Drugs: INH, Chloramphenicol, Linozolid, penicillamine
- c) Alcohol
- d) Copper deficiency
- e) Zinc and lead toxicity

- A) Were the bone marrow findings a sign of a neoplastic clonal process or induced by one the numerous medications/supplements she had used?
- B) Were the elevated platelets a part of an underlying myeloid neoplasm or a reactive process?
- C) Are we dealing with a myel***proliferative*** neoplasm or a myel***dysplastic*** syndrome. Could it be one transforming into another?
- D) What is her prognosis from the underlying hematological condition?
- E) Should we worry about thrombotic risk from thrombocytosis?
- F) How to optimize the management of her anemia and minimize transfusion requirements after she has failed erythropoietin?
- G) Is chelation therapy needed for iron overload?
- H) How to do all of the above in a recent immigrant from Mexico with limited access to resources.

Were the bone marrow findings and thrombocytosis a sign of a neoplastic clonal process or induced by one of her medications?

Mutations affecting the SF3B1 gene are frequent in myeloid neoplasms with ring sideroblasts. *

Next generation sequencing of a myeloid gene panel** identified presence of SF3B1 mutation on Exon 14 (c1986C>A) in our patient (VAF 26%).

*Yoshida et al. Frequent pathway mutations of splicing machinery in myelodysplasia. Nature 2011

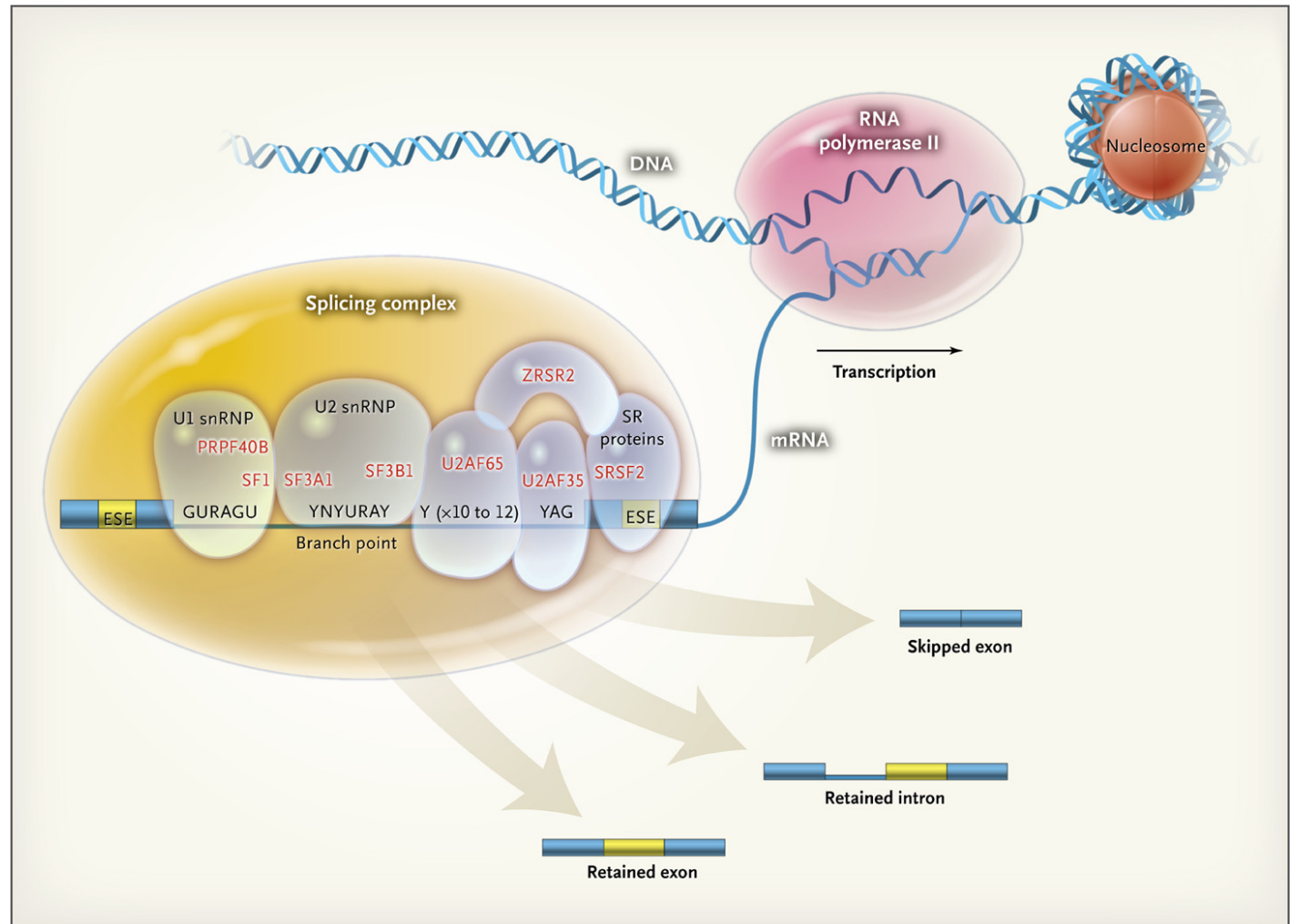
**ASXL1, CALR, CBL, CEBPA, CSF3R, DDX41, DNMT3A, EZH2, FLT3, GATA1, IDH1, IDH2, JAK2, KDM6A, KIT, KRAS, MPL, NPM1, NRAS, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, WT1 and ZRSR2

SF3B1 and other spliceosome mutations are identified in 80% of myeloid neoplasms with RS providing an easy tool to distinguish clonal from non-clonal processes.

Its demonstration established the clonal nature (neoplastic) of our patients thrombocytosis and bone marrow findings.

Her overall clinical and pathological findings were most consistent with a provisional entity called **Refractory anemia with ring sideroplasts and thrombocytosis** under the 2008 4th edition of WHO classification of myeloid neoplasms.

2016 revision of the 4th Edition includes it as a distinct entity called **Myelodysplastic/myeloproliferative neoplasm-ring sideroblasts-thrombocytosis**.



Ebert B, Bernard OA. N Engl J Med 2011;365:2534-2535.

B. What is her prognosis from the underlying hematological disease?

International Prognostic Scoring System (IPSS) for MDS

Variable	0	0.5	1	1.5	2
Bone marrow blasts (%)	<5	5-10		11-20	21-30
Cytogenetics	Good	Intermediate	Poor		
Cytopenias	0/1	2-3			

Risk Group	IPSS score	Median survival
Good	0	5.7
Intermediate-1	0.5-1	3.5
Intermediate-2	1.5-2	1.2
High	2.5-3	0.4

Karyotype definition.

Good: normal, -Y, del(5q), del(20q)

Poor: Complex (≥ 3), chromosome 7

Intermediate: all other

Cytopenia definition.

RBC: Hb < 10gm/dl

WBC: neutrophils < 1800/mcl

Platelets: < 10,000/mcl

Revised International Prognostic Scoring System (IPSS-R) for MDS

Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very poor
Bone marrow blasts (%)	≤2		>2 to <5		5-10	>10	
Hb (g/dl)	≥10		8-10	<8			
Neutrophil (cells/mcl)	>0.8	≤0.8					
Platelets(cells/mcl)	≥100	50-100	≤50				

Risk group	IPSS-R	Survival
Very low	≤1.5	8.8
Low	>1.5 to 3	5.3
Intermediate	>3 to 4.5	3
High	>4.5 to 6	1.6
Very high	>6	0.8

Karyotype definition.

Very Good: -Y, del (11q)

Good: normal, del (12p), del(5q), del (20q)

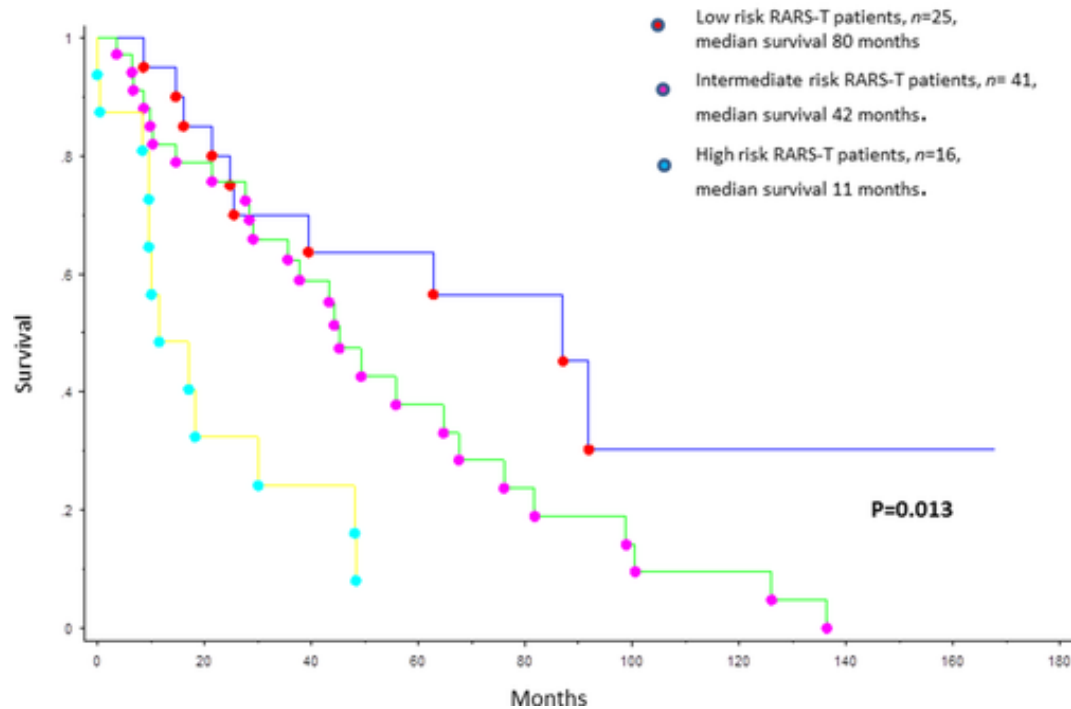
Intermediate: del(7q), +8, +19, i(17q), any other clones

Poor: -7, inv(3), complex 3 abnormalities.

Very poor: complex > 3 abnormalities.

Predictors of survival in refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) and the role of next-generation sequencing

Over-all survival of 82 patients with RARS-T, stratified by the Mayo Clinic RARS-T prognostic model.



Variable	Points
Abnormal karyotype	2
SETBP1 and/or ASXL1 mutation	1
Hb < 10gm/dl	1

Risk Group	Points	Median OS (months)
Low	0	80
Intermediate	1	42
High	2 and higher	11

Thrombotic risk in MDS/MPN-RS-T (Mayo clinic data)

- 21% risk of thrombotic episode during the duration of the disease (19% venous and 2% arterial)
- Hb < 10gm/dl, presence of SF3B mutation and prior history of thrombosis contributed to risk of thrombosis
- Cardiovascular risk factors, JAK2 mutation status and age did **NOT** increase thrombosis risk

How to optimize the management of her anemia and minimize transfusion requirements after she had failed erythropoietin?
How to minimize her thrombotic risk?

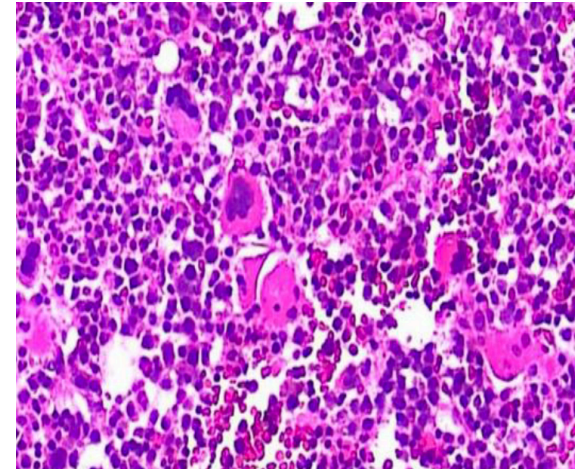
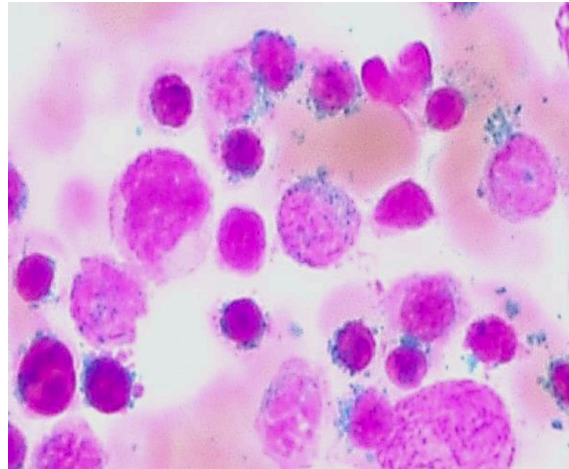
- a) Continue erythropoiesis stimulating agents (ESA) and add GCSF?
- b) Lenalidomide, with or without ESA?
- c) Try androgenic steroids like danazol?
- d) ESA, lenalidomide and androgeneic steroids have inherent thrombotic risk. Will the risk be prohibitive in a patient with clonal thrombocytosis?
- e) Hypomethylating agents?
- f) Prophylactic anti-platelet or anti-coagulants.

Treatment history:

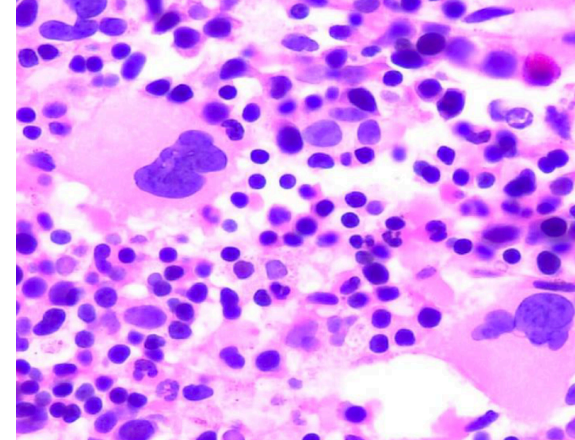
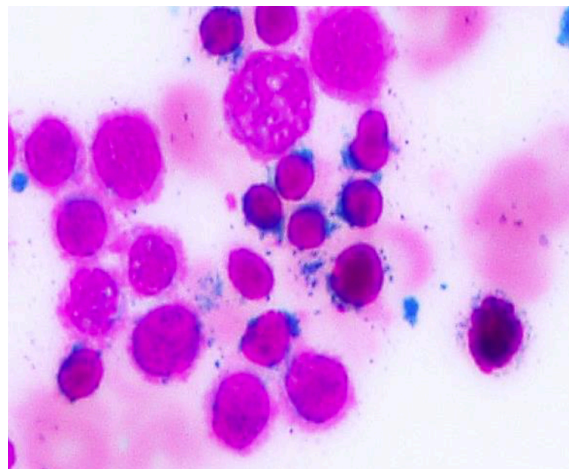
- A. Azacitidine 75mg/m² sq for 5 days, repeated every 28 days for 4 cycles (April to August 2015).
- B. Darbepoitin 300mcg sq every 2 weeks (Ongoing since April 2015)
- C. Enteric coated aspirin 81mg (Ongoing since April 2015)

Bone marrow biopsy was repeated after completing 4 cycles of azacytidine and showed no major changes in the cellularity or % RS

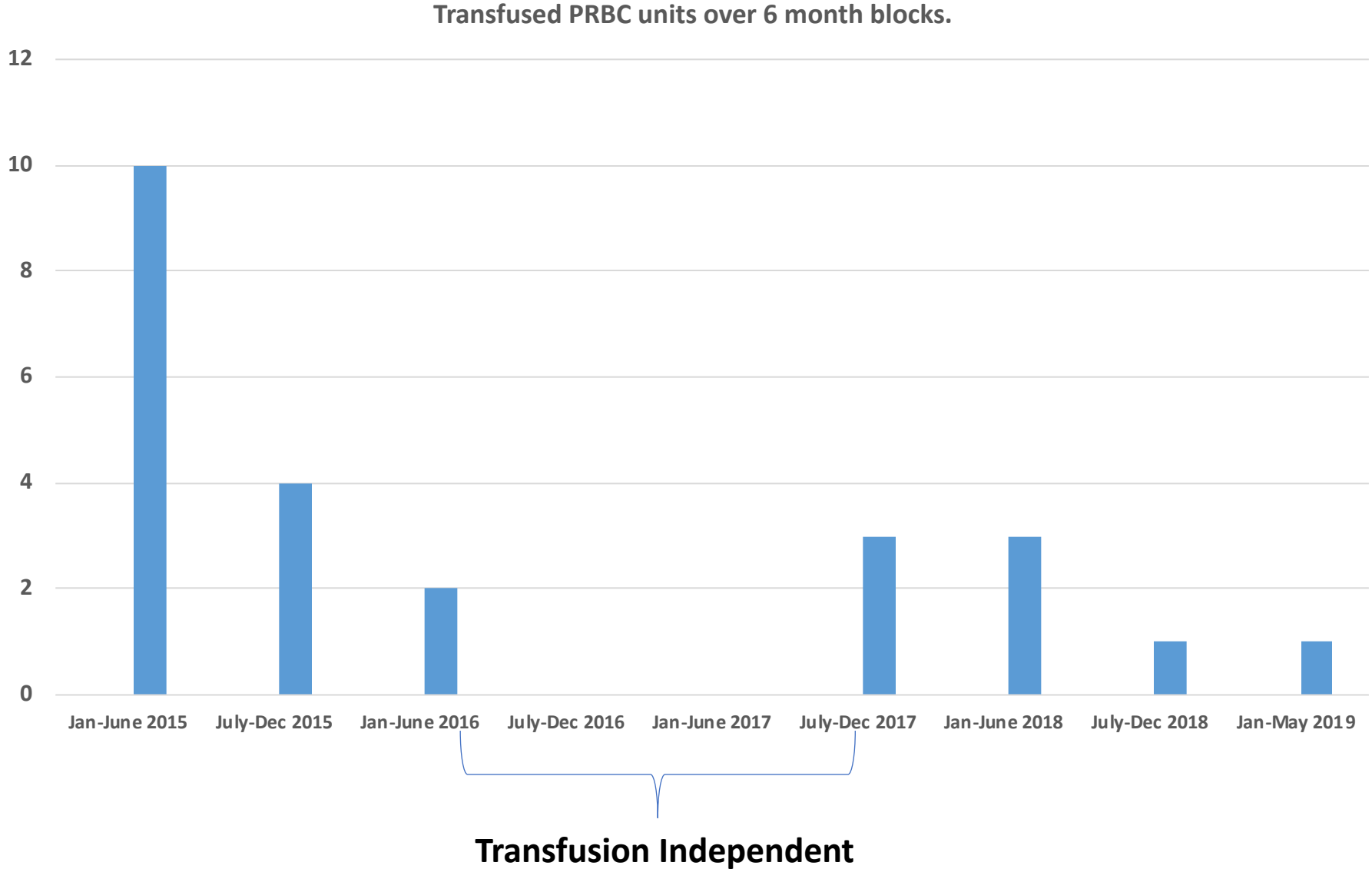
Jan 2015



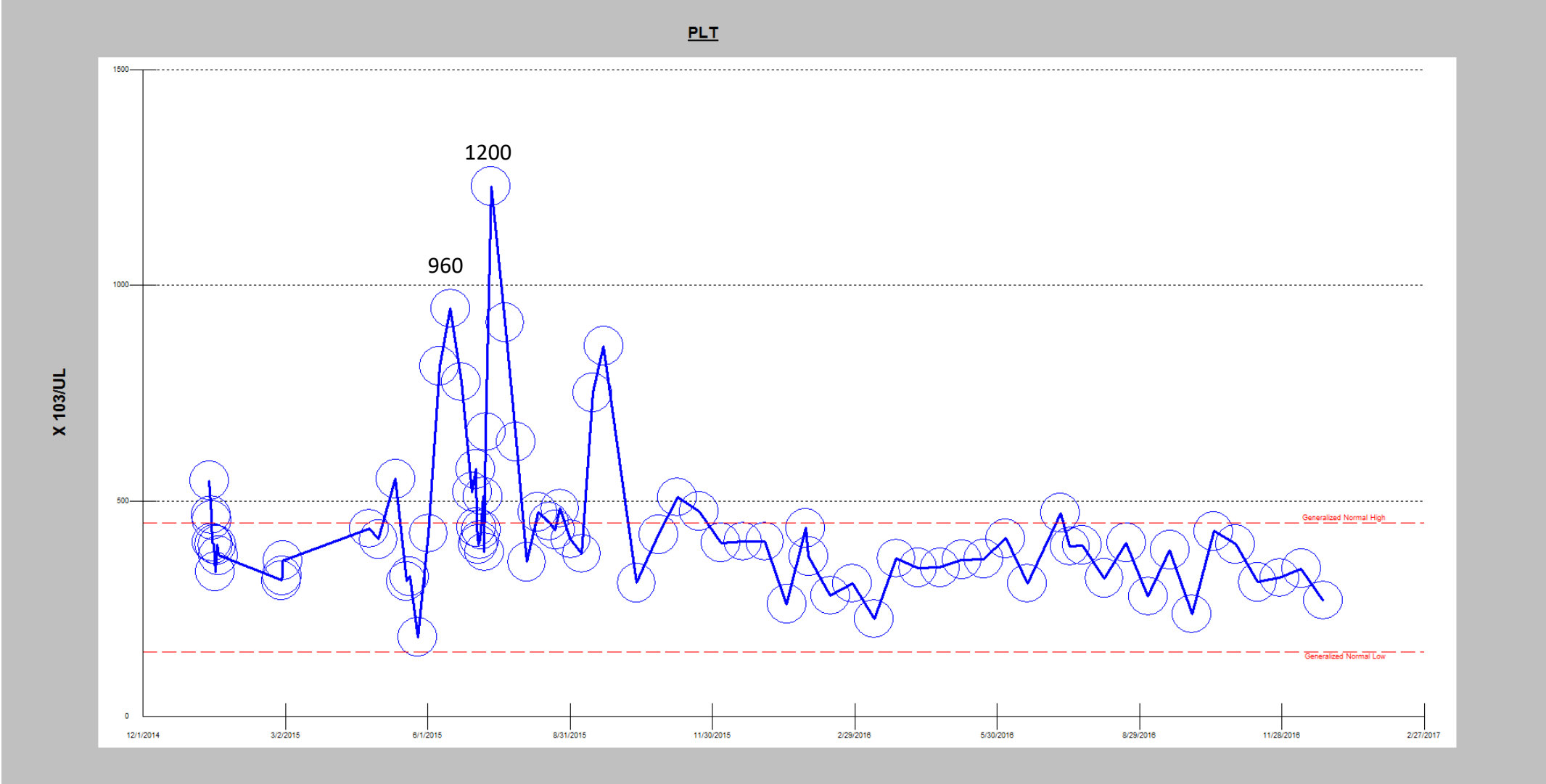
Sep 2015



Transfusion requirements (Jan 2015- June 2019).



Trend in platelet counts for 2015-2016



What about the iron overload?

Ineffective erythropoiesis and frequent transfusions contribute to iron overload.

Increased non-transferrin bound iron combines with oxygen to generate free radicals causing lipid peroxidation, protein and DNA damage.

Iron status can be monitored non-invasively with serum ferritin levels and T2 MRI of liver and heart.

National guidelines suggest using chelation therapy in low risk MDS if transfusions requirements have been more than 20 units, and/or ferritin levels are more than 2500ng/ml

Effective chelation improves overall survival and cardiac and endocrine function in patients with thallemia.

“Neither serum ferritin nor the number of red blood cell transfusions affect overall survival in refractory anemia with ringed sideroblasts”
Chee C, Tefferri A et al. Am J Hematol 2008; 83: 611-613

Retrospective review of 126 cases of RARS

In multivariate model, ***overall survival was not affected by number of RBC units transfused*** over the disease course.

No correlation between survival and serum ferritin at diagnosis or follow up.

No difference in survival when patients were stratified based on serum ferritin <1000ng/ml, 1000-5000ng/ml or >5000ng/ml.

WHO-defined 'myelodysplastic syndrome with isolated del(5q)' in 88 consecutive patients: survival data, leukemic transformation rates and prevalence of JAK2, MPL and IDH mutations. Patnaik MM, Tefferri A et al. Leukemia 2010; 7:1283-1289

Sixty patients with WHO defined MDS with isolated del(5q) were followed from diagnosis to death (Median 6.6 years).

Number of deaths attributed to iron overload: Zero

Survival did not correlate with serum ferritin.

Available iron chelators, *handle with caution.*

Deferoxamine:

- a) Requires daily parenteral administration
- b) Hearing loss and visual side effects.

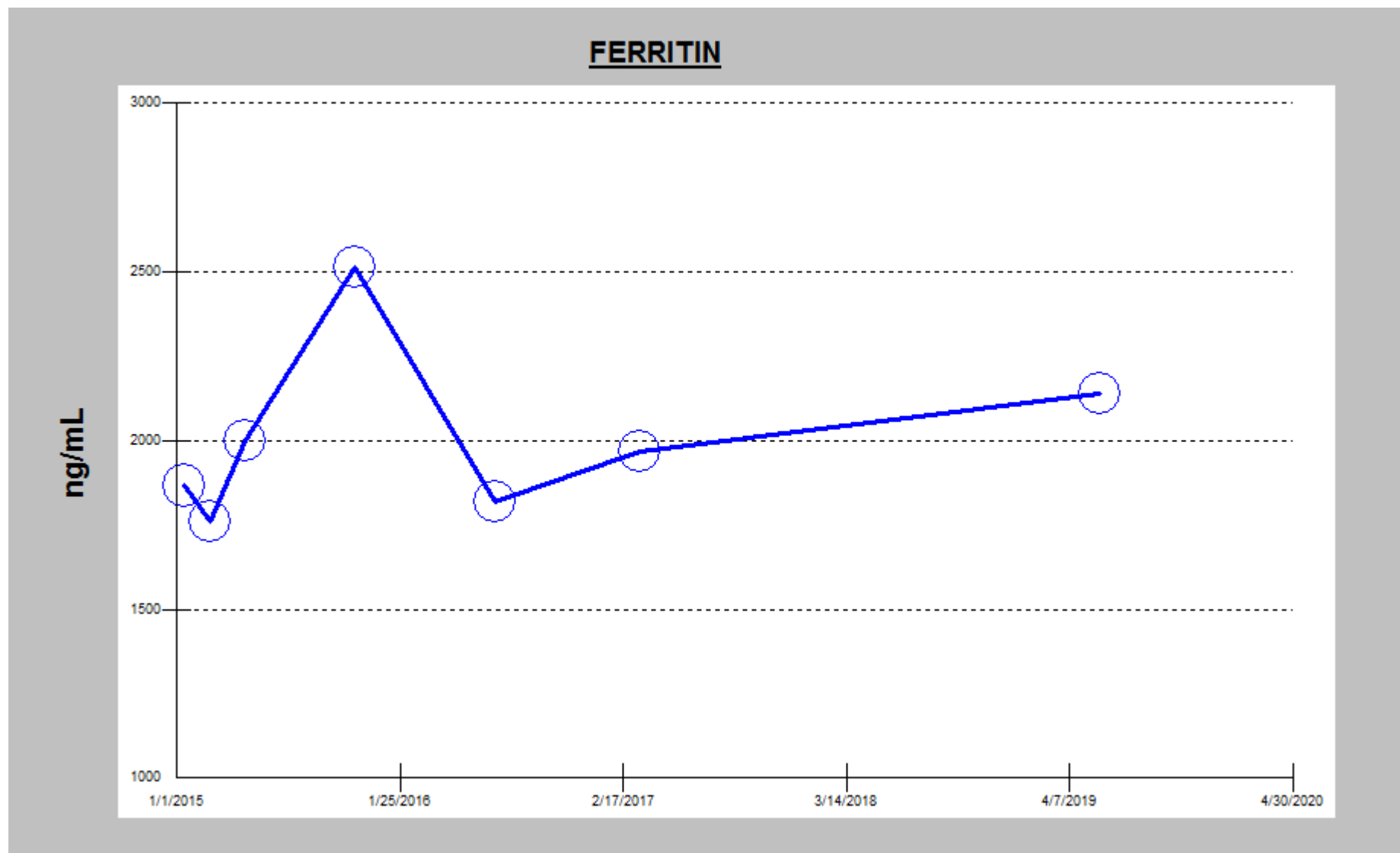
Deferiprone:

- a) GI side effects
- b) Agranulocytosis

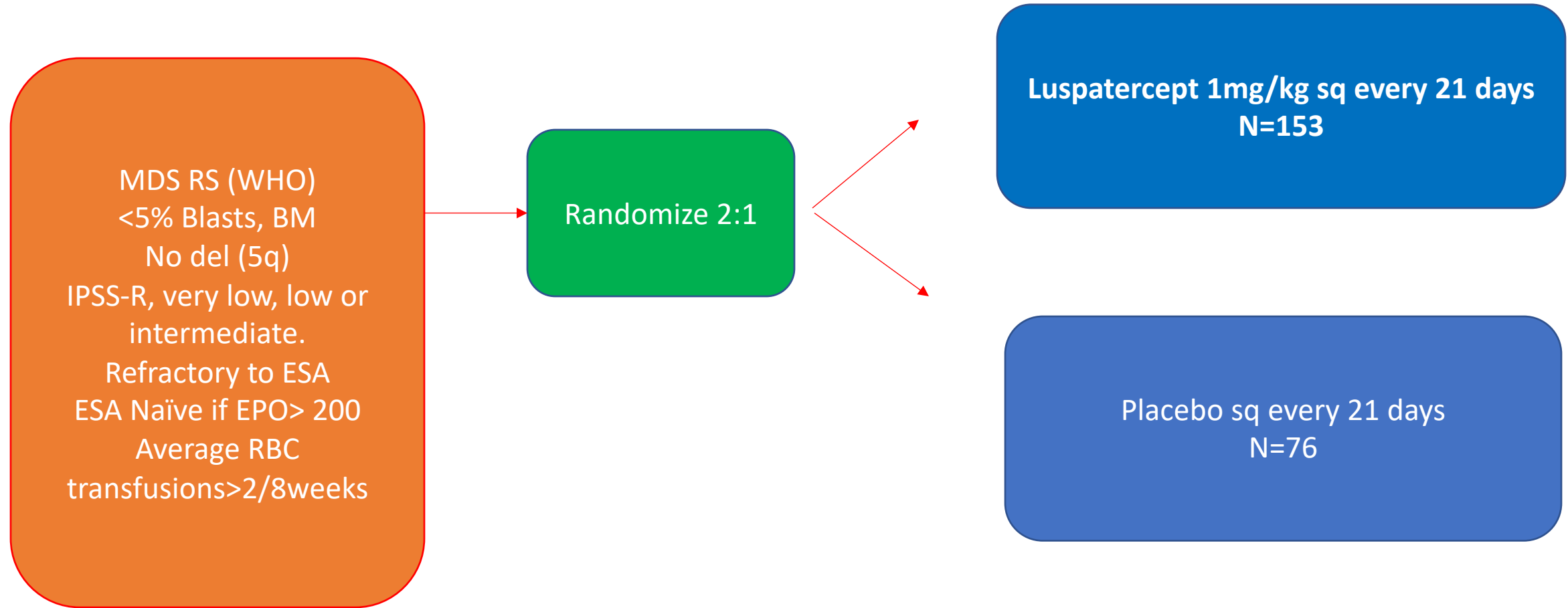
Deferasirox:

- a) Renal failure
- b) Hepatic failure
- c) Cytopenias
- d) GI side effects

Patient has not initiated iron chelation therapy.



MEDALIST Trial: A Randomized phase III, placebo controlled study of Luspatercept (TGF-beta inhibitor)



MEDALIST Trial: Transfusion independence at 8 weeks

Luspatercept (n=153)	Placebeo (n=76)	P
58 (37.9 %) 95% CI 30.2-46.1	10 (13.2%) 95% CI 6.5-22.9	<0.0001

Case 2*

82 year old male presented in Dec 2014 with fatigue and popliteal vein DVT. Exam remarkable for conjunctival pallor, irregular heart rhythm and swollen left leg.

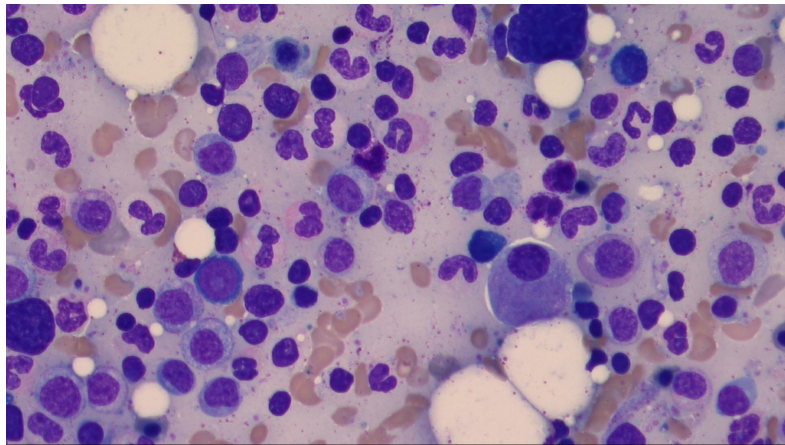
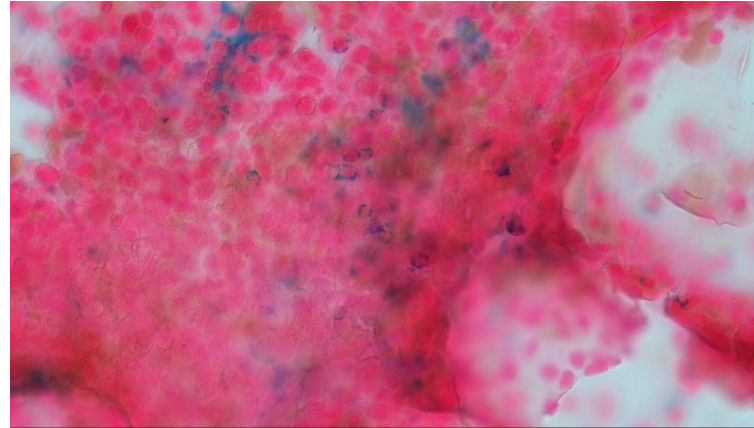
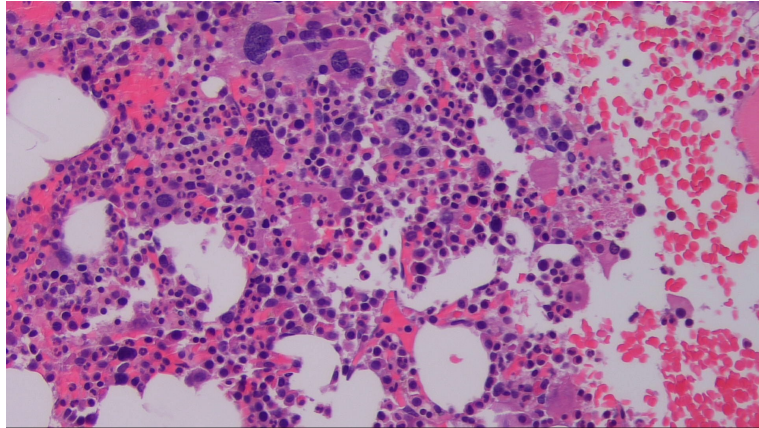
Labs

WBC 9600/mcl , N 66%, L30%, Mo 1%, Eo 2%

Hb 9.9gm/dl, with MCV of 108fl

Platelets **986,000/mcl**

Bone marrow biopsy



Hyper-cellular bone marrow

Blasts:1-2%

15-20% RS

Megakaryocytes: increased, small in size.

Karyotype and molecular studies



Molecular studies

CALR exon 9 frame shift mutation (c1103_1130del37) detected.

JAK2 negative
BCR/ABL negative
SF3B negative
CSF3R negative
SRTBP1 negative
MPL negative

Community management

Diagnosis: MPN (CALR mutation and thrombocytosis, possibly ET)

Emergent platelet-pheresis and anticoagulation with warfarin.

Hydroxyurea was started to control the thrombocytosis however led to worsening anemia. Anagleride was tried but patient could not tolerate the cardiovascular effects. Ruxolitinib (JAK inhibitor) was prescribed. Patient remained transfusion dependent for 2015.

He resides in Van Horn and was having difficulty juggling need for transfusion support with the need to control his platelet counts. He sought a second opinion with us in Jan 2016.

Does he have MDS/MPN-RS-T?

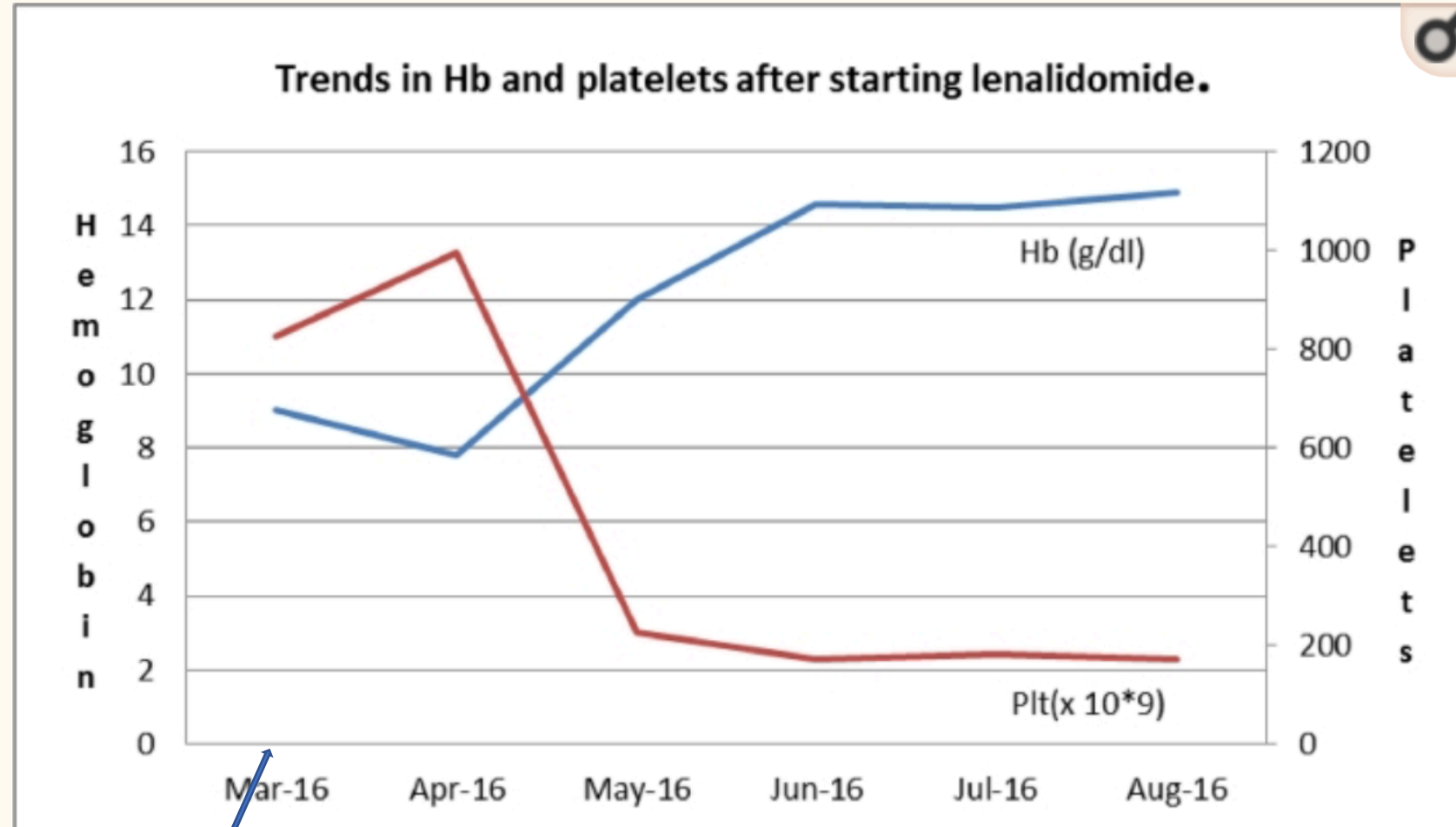
- Anemia associated with erythroid lineage dysplasia without multilineage dysplasia, $\geq 15\%$ RS, $< 1\%$ blasts in peripheral blood and $< 5\%$ blasts in the bone marrow.
- Persistent thrombocytosis with platelet count $\geq 450 \times 10^9/L$
- Presence of SF3B1 mutation, or in the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy to account for the MDS/MPN features.
- No BCR-ABL1 fusion gene, no rearrangement of PDGFRA, PDGFRB or FGFR1; or PCM1-JAK2; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)
- No preceding history of MPN. MDS (except MDS-RS) or other type of MDS/MPN.

Does he have MDS with isolated del(5q)

	WHO 4th Edition	2016 Update of 4 th edition
Cytopenias	1-2	1-2
Dysplastic lineage	1-3	1-3
Blasts	BM <5% PB<1% No Auer rods	BM <5% PB<1% No Auer Rods
Cytogenetics	Isolated del (5q)	del (5q) with <i>upto one additional cytogenetic</i> abnormality except - 7/del(7q)

Mitelman database showed only 15 case reports of RS morphology with isolated del(5q)
 Mutations in JAK2/MPL and CALR are frequent in MDS/MPN-RA-T but rare in MDS with isolated del (5q).

Patient was more interested in the management of the disease, than the name of the disease. Ruxolitinib was stopped. Lenalidomide was prescribed.



Lenalidomide initiated

Summary

- Clinicians continue to encounter myeloid neoplasms which defy clear categorization.
- Integration of clinical data, pathology findings, cytogenetics and molecular studies is crucial.
- Even for cases where there is no final consensus on terminology, reasonable therapeutic decisions can be made in the vast majority of cases.

**Medicine is a science of uncertainty
and an art of probability.**

Sir William Osler.