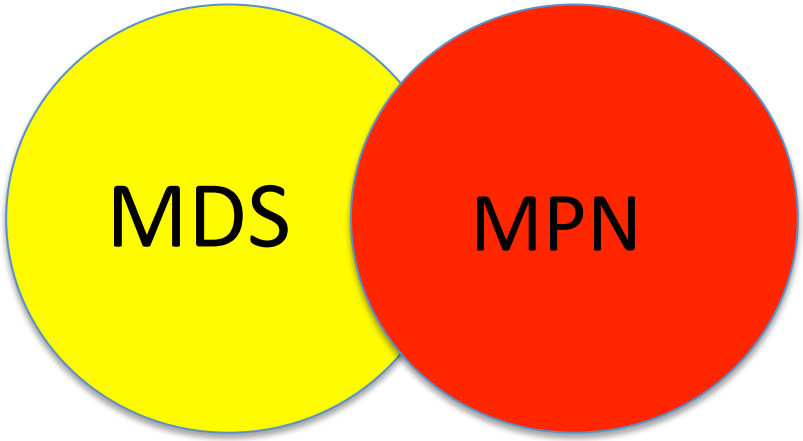
MDS/MPN: What it is and How it Should be Treated?



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MDS Foundation Patient & Family Forum: May 20, 2017

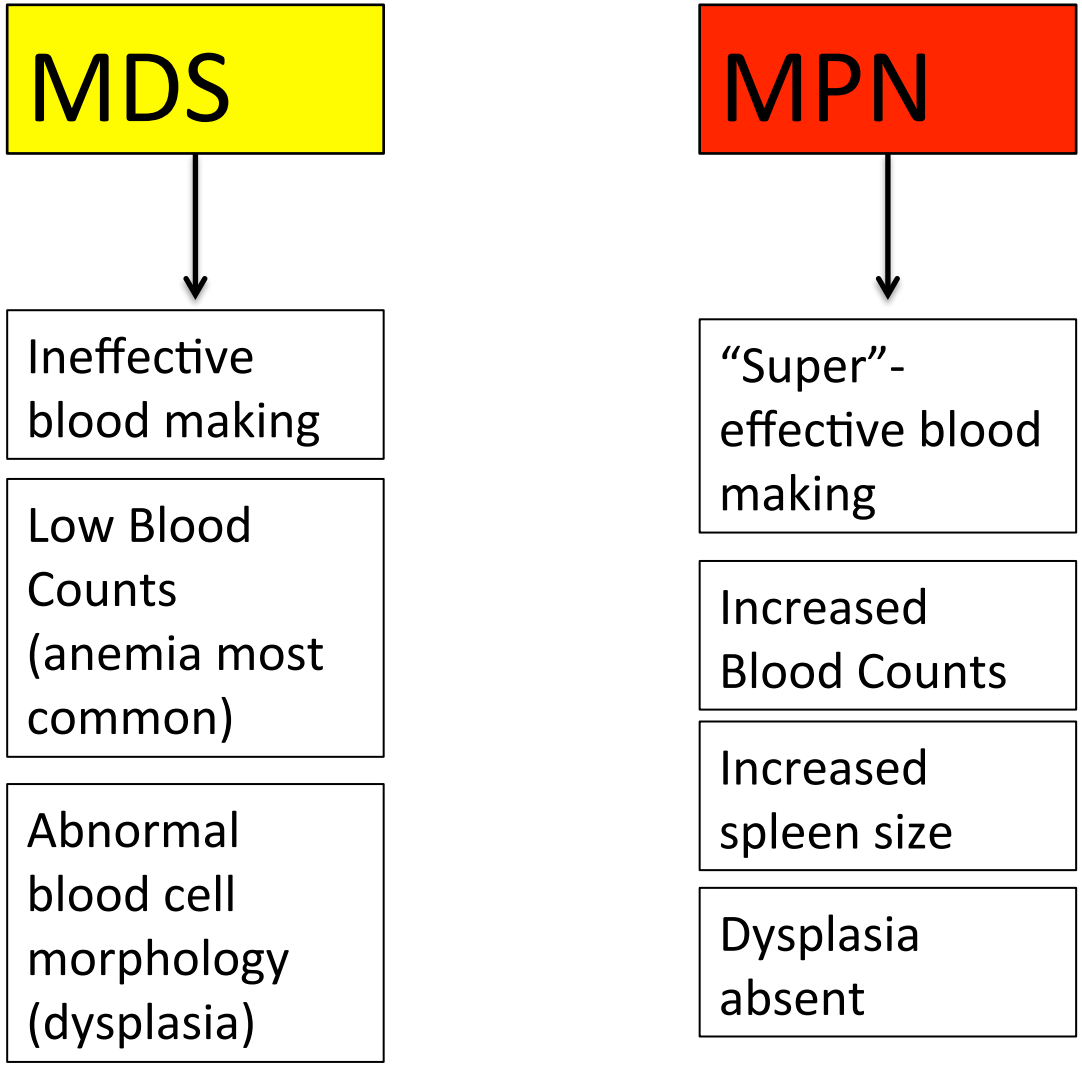
What is a myeloproliferative neoplasm (MPN)?

- Myeloproliferative neoplasms are diseases in which the bone marrow makes **too many** red blood cells, platelets, or certain white blood cells.
- Common Symptoms include:
  - Headache
  - Shortness of breath
  - Bleeding
  - Dizziness
  - Itchiness
  - Fatigue
  - Weakness
  - Abdominal pain from an enlarged spleen

Symptoms of MPN

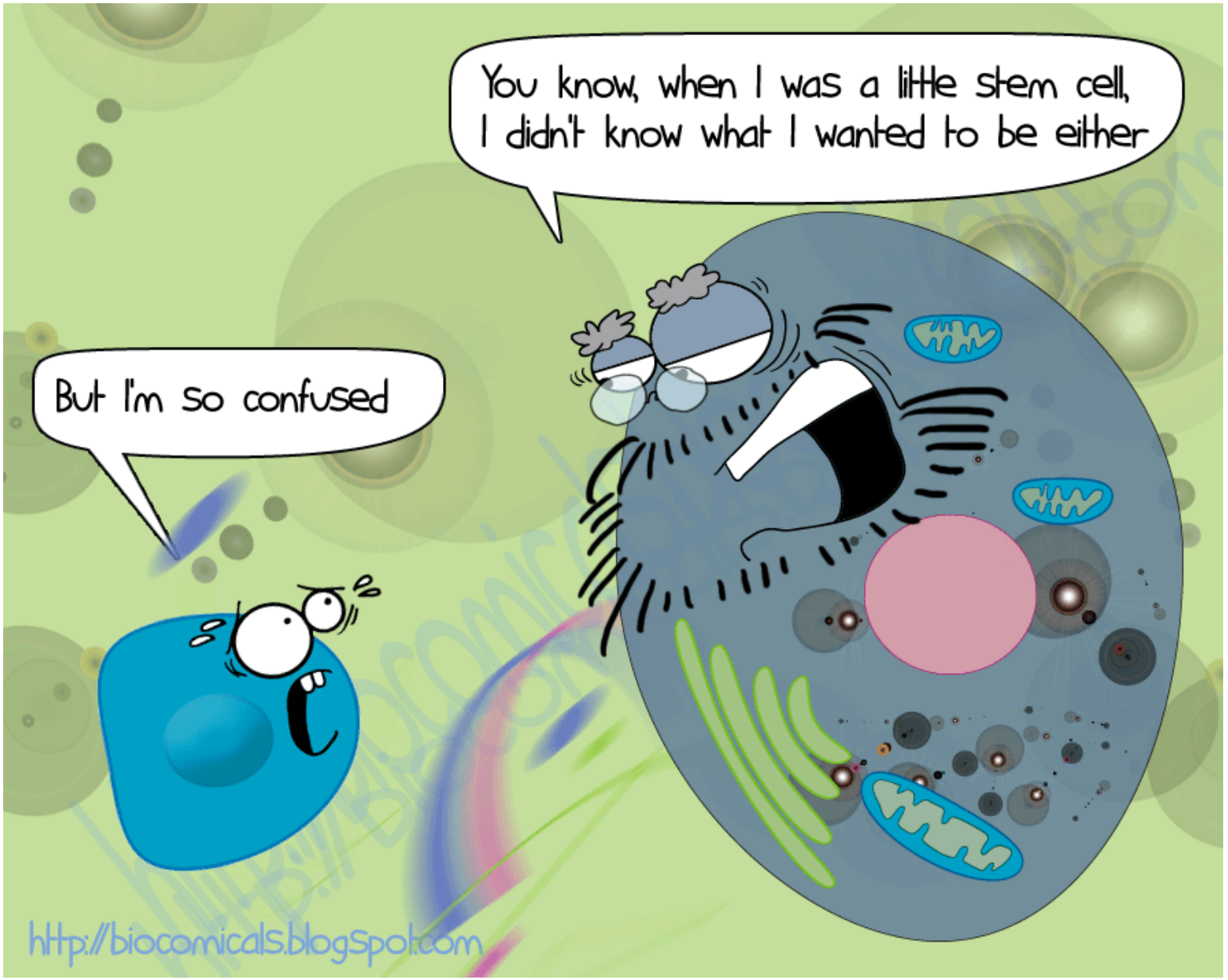
- Common myeloproliferative neoplasms include:
  - **Chronic Myeloid Leukemia**-overproduction of white cells
  - **Polycythemia Vera**-an overproduction of red blood cells
  - **Essential Thrombocythemia**-overproduction of platelets
  - **Chronic Neutrophilic Leukemia**-overproduction of neutrophils (a type of white cell)
  - **Chronic Eosinophilic Leukemia**-overproduction of eosinophils (a type of white cell)
  - **Primary Myelofibrosis**- a condition in which bone marrow tissue is gradually replaced by fibrous scar-like tissue, disrupting normal blood cell production.

Comparison of Features of MDS vs. MPN



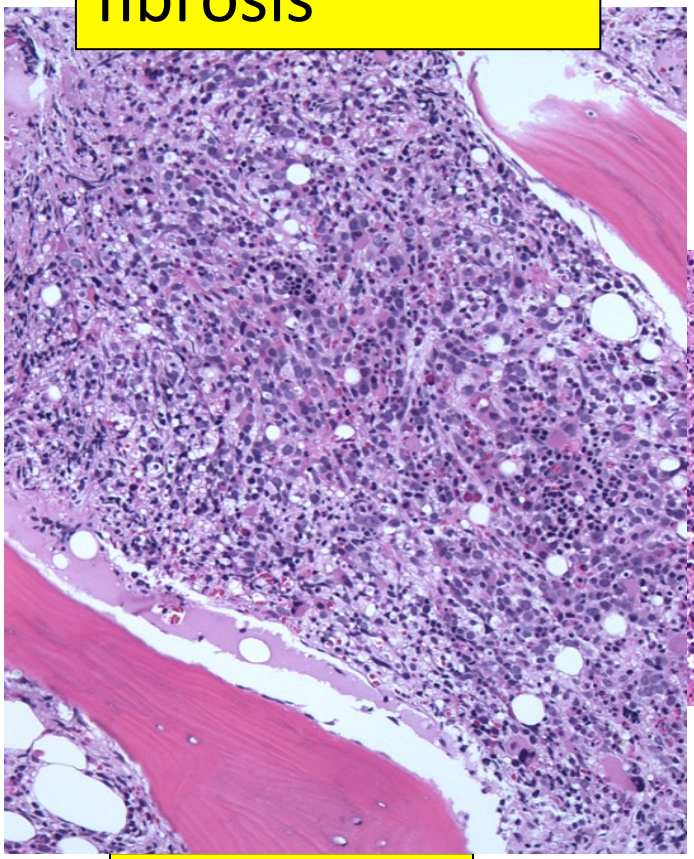
What is MDS/MPN?

- Some problems with blood-cell formation have features of both MDS and MPN.
- Best defined entities include:
  - Chronic Myelomonocytic Leukemia (CMML)
  - Atypical Chronic Myeloid Leukemia (aCML)
  - Juvenile Myelomonocytic Leukemia (JMML)
  - MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN- RS-T)
  - MDS/MPN unclassifiable (MDS/MPN-U)


You know, when I was a little stem cell, I didn't know what I wanted to be either
But I'm so confused
http://biocomicals.blogspot.com

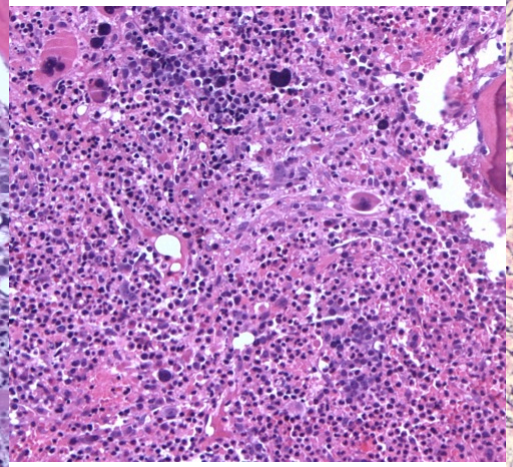
Pathologists' Challenge

"Dysplasia with fibrosis"

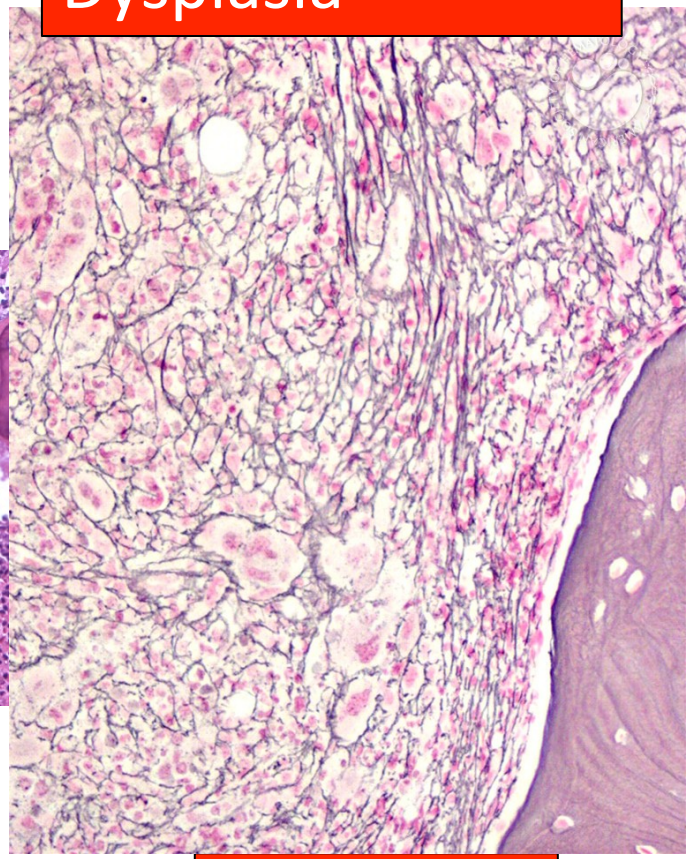


MDS

MDS/MPN



"Fibrotic with Dysplasia "



MPN

CMML

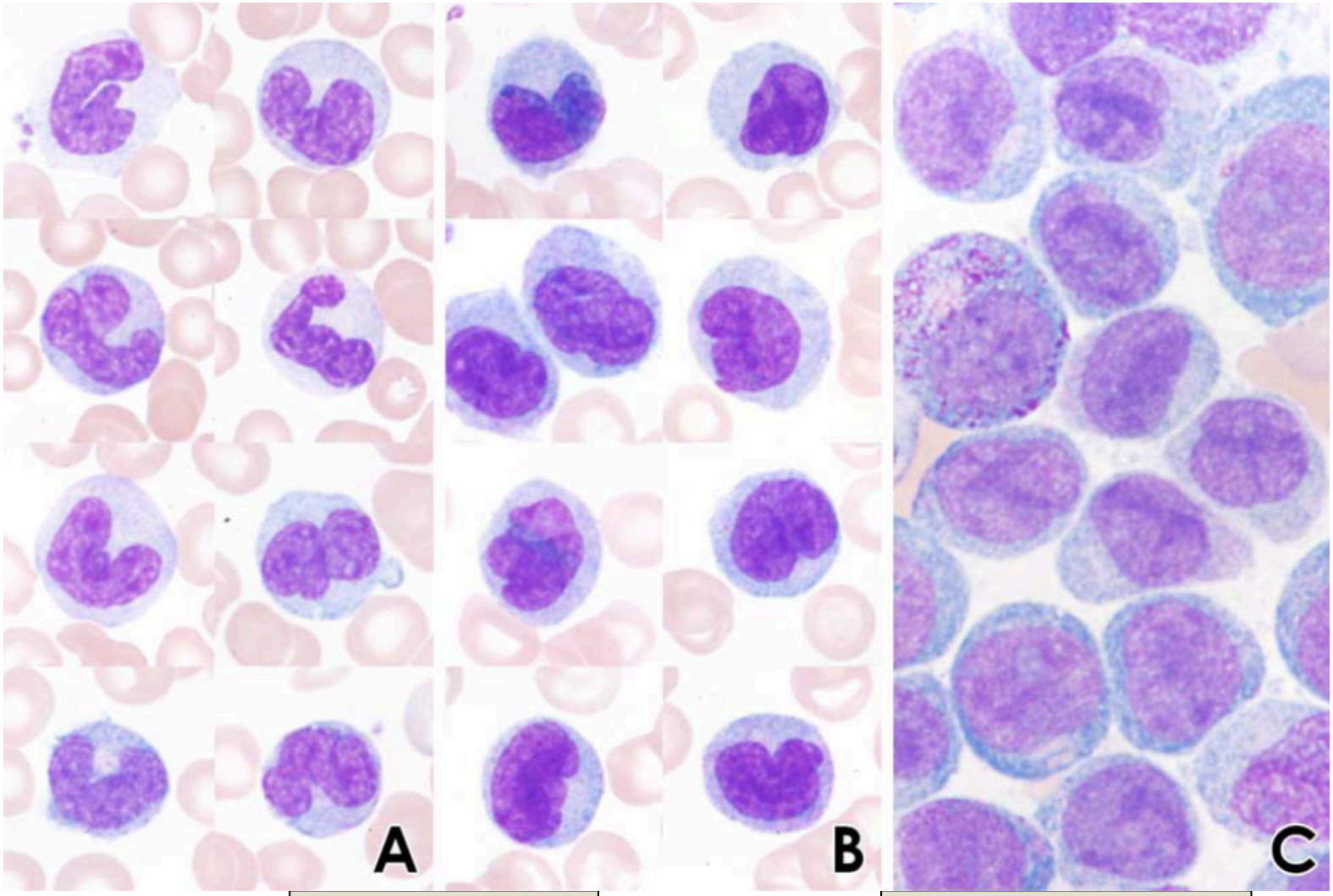
CMML

- Most common of MDS/MPN entities
- Main features is too many monocytes in your blood (at least 1,000 per mm3)
- Bone marrow is **hypercellular** with monocytosis.
- Dysplasia ≥ 1 cell line but < 20% blasts
- Spleen is often enlarged
- 15-30% of patients go on to develop AML.
- Gene mutations are seen in >90% of patients
  - *TET2* ~60%
  - *ASXL1* ~40%
  - *SRSF2* ~50%
  - *RAS* ~30%
  - *CBL* ~15%

Symptoms of CMML

- Having too many monocytes also causes many of the symptoms of CMML.
- These monocytes can settle in the spleen or liver, enlarging these organs.
- Weight loss, fever, and loss of appetite
- Low blood counts

Diagnosis of CMML



Peripheral Blood

Bone Marrow Aspirate

Staging of CMML

- CMML can be divided into 3 categories by blood and marrow blasts count.
  - CMML-0 blood < 2%; marrow <5%
  - CMML-1 blood 2-4% marrow 5-9%
  - CMML 2 blood 5-19% marrow 10-19%
- WBC Count
  - MDS CMML ≤ 13,000
  - MF CMML > 13,000
- Other poor prognostic features include:
  - Hb < 10
  - Platelet Count < 100
  - Abnormal chromosomes (monosomy 7 or complex)
  - ASXL1 mutation

From Cazzola *et al*, *Hematology Am Soc Hematol Educ Program*, 2011

Prognosis in CMML

Subtype	Overall Survival (Months) n=386	Overall Survival (Months) **CMML/MDS** n=204	Overall Survival (Months) **CMML/MPN** n=182	P-value	AML Progression at 2 years
CMML-0 <5% blasts n=101	31	**48**	**17**	.03	**7%**
CMML-I 5-9% blasts n= 204	19	**29**	**15**	.008	**18%**
CMML-2 10-19% blasts n=81	13	**17**	**10**	.09	**36%**

*WBC ≤ vs >13,000 (CMML/MDS vs CMML/MPN)

Schuler et al, Leuk Res 2015

Treatment of CMML

- Most common treatment is Azacitadine or Decitabine
- Overall response rate: 30-40%[1] (up to 70%)
- Complete remission rate: 10-58%
- Overall Survival (OS): 12-37 months
- Prognostic factors in pts treated with Azacitidine
  - Worse OS: BM blasts >10% and WBC >13 x 10^9/L [2]
  - Better OS: Absolute monocyte count <10 x 10^9/L and PB blasts <5% [3]

[1] Patnaik and Tefferi, *Am J Hematol*, 2016
[2] Ades *et al*, *Leuk Res*, 2013
[3] Fianchi, *et al*, *Leuk Lymphoma*, 2013

Transplantation is only cure for CMML

- No randomized trials
- Increasing use of reduced intensity conditioning
  - Other donor sources: haploidentical; double umbilical cord
- Fred Hutch Study (n=85)[1]
  - 10-yr overall and relapse-free survival: 40% and 38%, respectively
  - Increasing age, higher co-morbidity index, and poor-risk cytogenetics were associated with increased mortality and reduced relapse-free survival
- CMML at EBMT (n=513; 95 pts with sAML)[2]
  - 4-year overall and relapse-free survival: 33% and 27%, respectively
  - In multivariate analysis, the only significant prognostic factor for survival was the presence of a complete remission at time of transplantation

[1]Eissa H et al, Biol Blood Bone Marrow Transplant, 2011
[2] Symeonidis *et al*, Br J Haematol, 2015

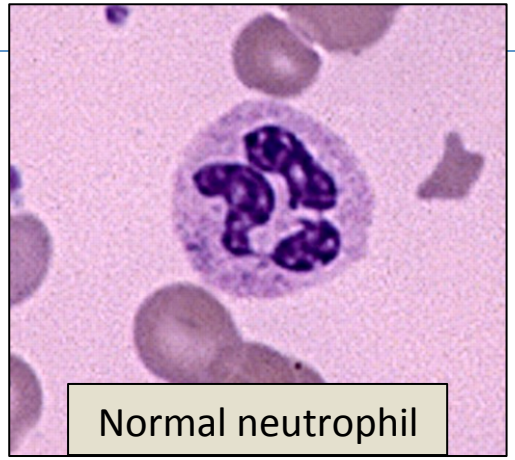
Atypical CML

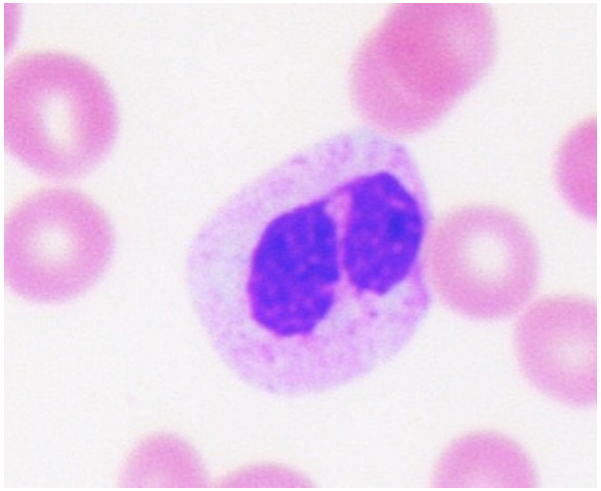
Atypical CML

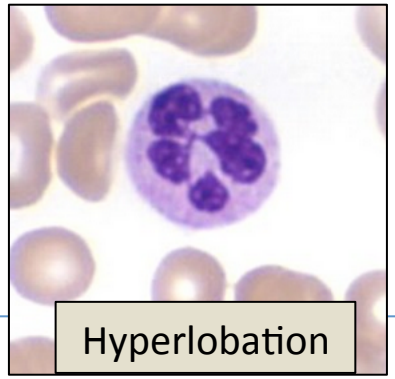
- Similar to CML but no Philadelphia chromosome = cannot treat with Gleevec or Tasigna
- < 2 cases for every 100 cases of CML
- Median age 70; Male predominance
- Symptoms: Fatigue, night sweats, splenomegaly
- Diagnosis is pathologic
  - too many neutrophils but no basophilia or monocytosis.
- Treatment of choice is bone marrow transplant.

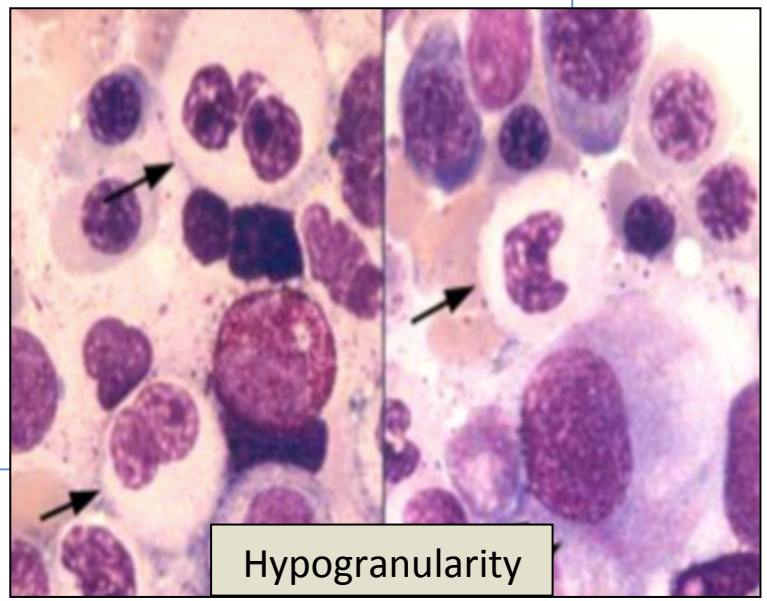
White Blood Cell Dysplasia (Dysgranulopoiesis)

- Hypogranularity
- Hypolobation
- Hyperlobation
- Pseudo-Pelger Huet cells

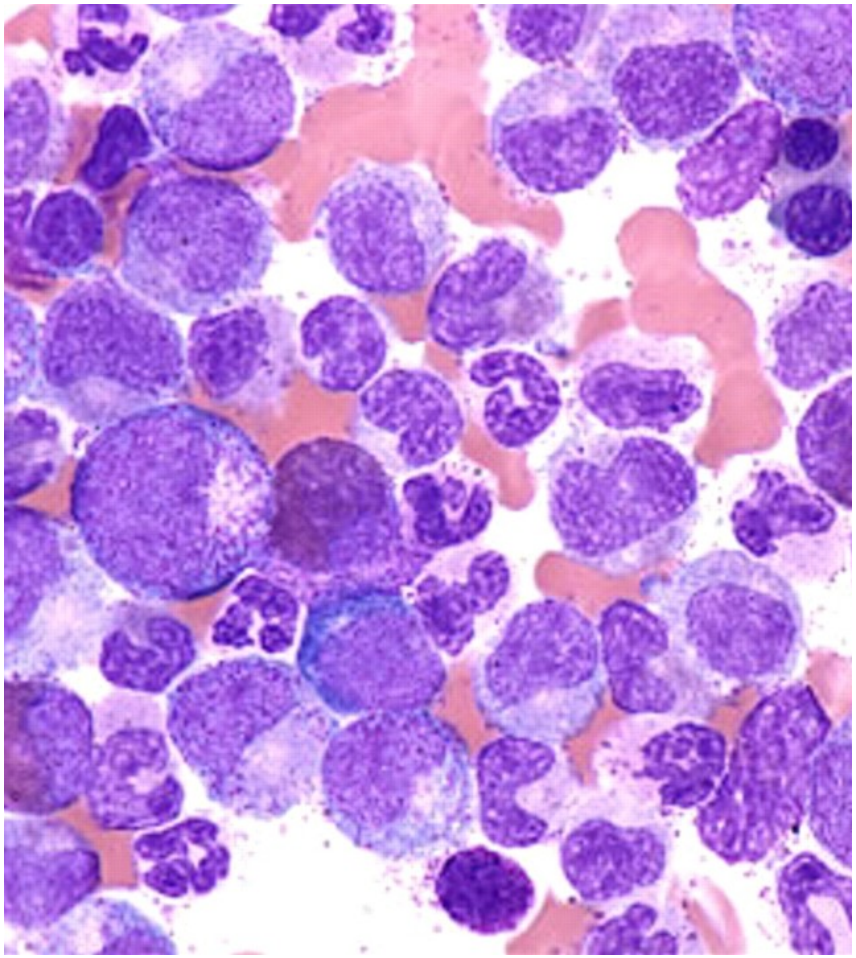

Normal neutrophil


Pseudo-pelger Huet; hypolobation

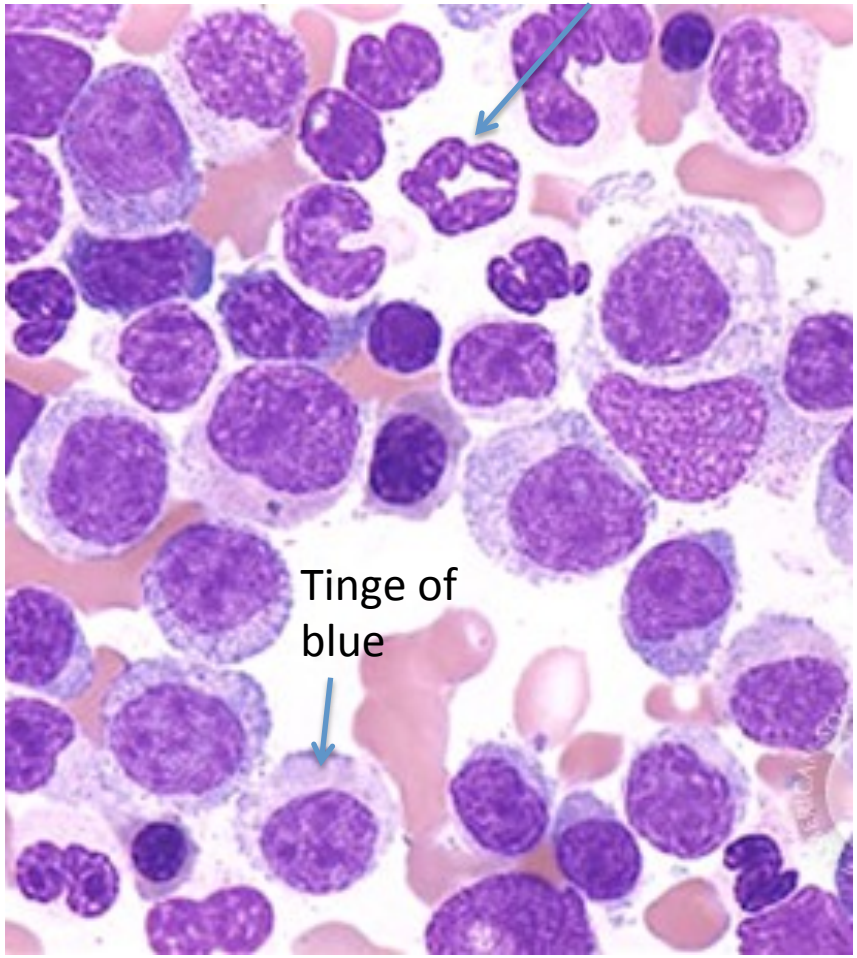

Hyperlobation


Hypogranularity

CML vs Atypical CML



CML



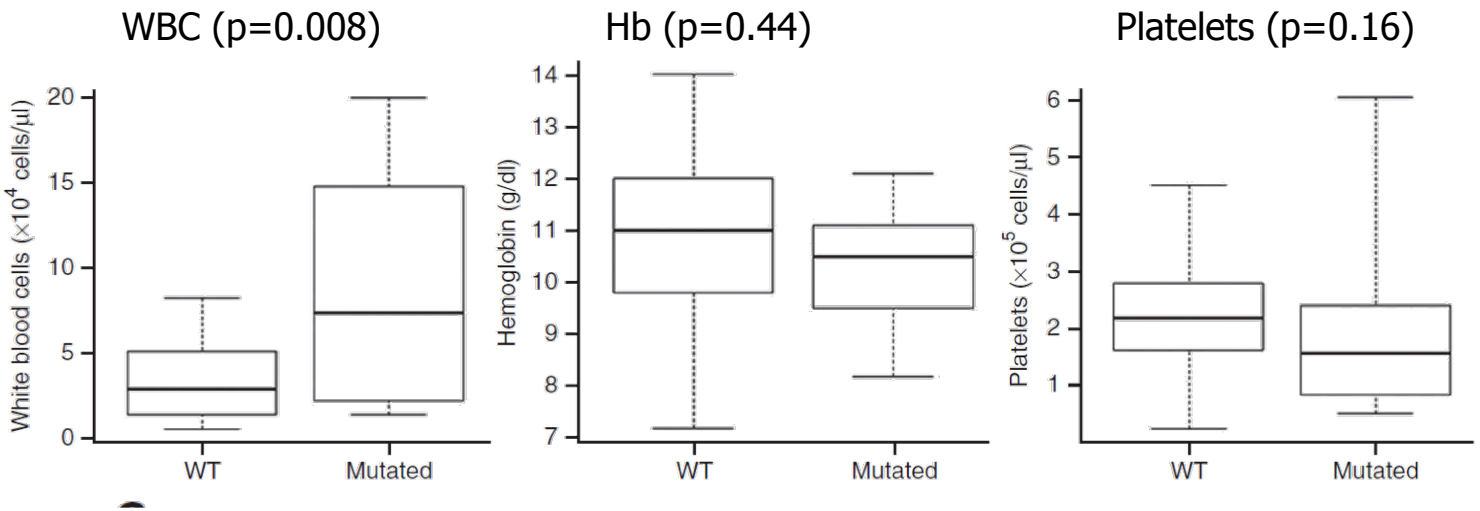
Atypical CML

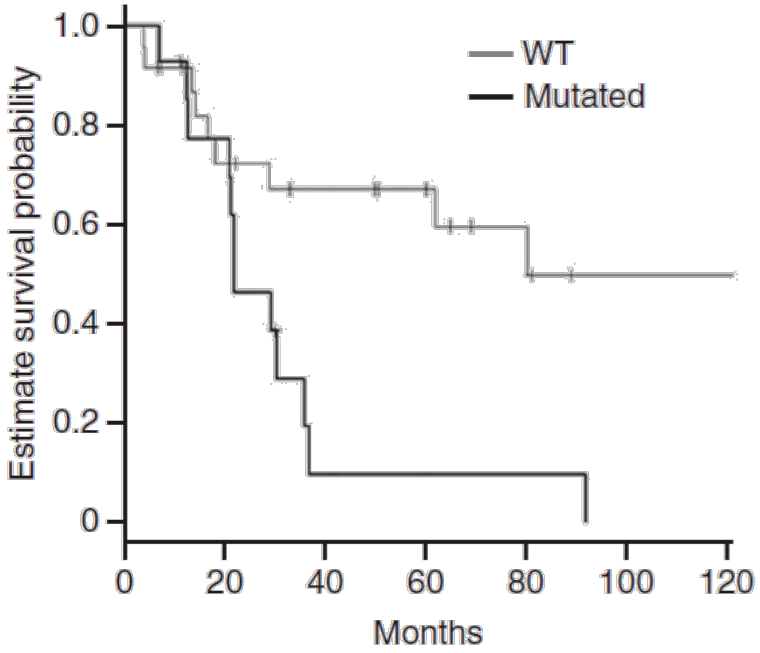
Atypical CML: Disease Course

- The largest series of WHO-defined aCML: 55 cases from an Italian cohort.
- Overall median survival: 25 months.
- Transformation to AML occurred in 22 patients (40%), with a median time from diagnosis of 18 months.
- Predictors of shorter survival:
  - Older age (>65 years)
  - Female gender
  - WBC count (>50x10^9/L)
  - Presence of immature circulating cells.

[1] Breccia *et al*, *Haematologica,* 2006

SETBP1 Mutation in 30% of Atypical CML





SETBP1-= 77 months
SETBP1+= 22 months

p=0.01

Piazza R. *et al*, Nat Genetics 2013

MDS/MPN-RS-T (RARS-T)

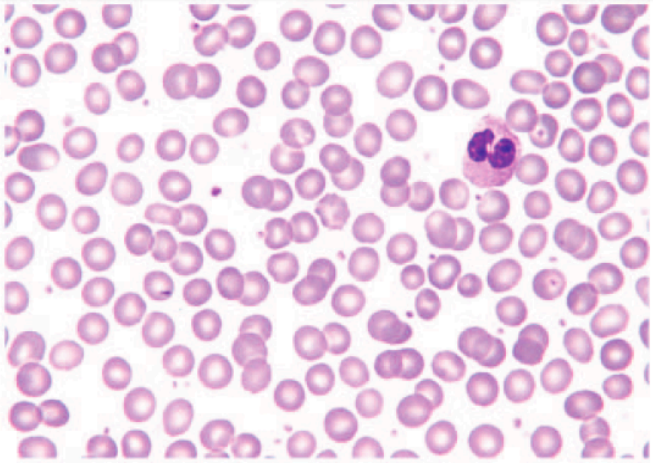
MDS/MPN RARS-T Symptoms

- Like RARS in MDS but with too many platelets (> 450,000).
- Patients can be divided into low risk (0 factors) and high risk (1 or 2 factors), based on age >60 years and history of blood clot.
- Low risk patients benefit from low dose aspirin therapy (81–100 mg).
- Bone marrow transplant is reserved for patients with blood counts not responding to transfusions or progressive disease.

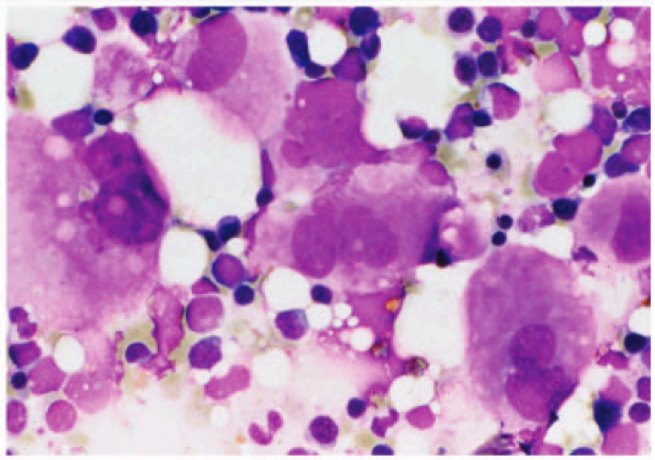
Pathologic features of MDS/MPN RARS-T

Peripheral blood:

Increased platelets & dysplastic neutrophil



A



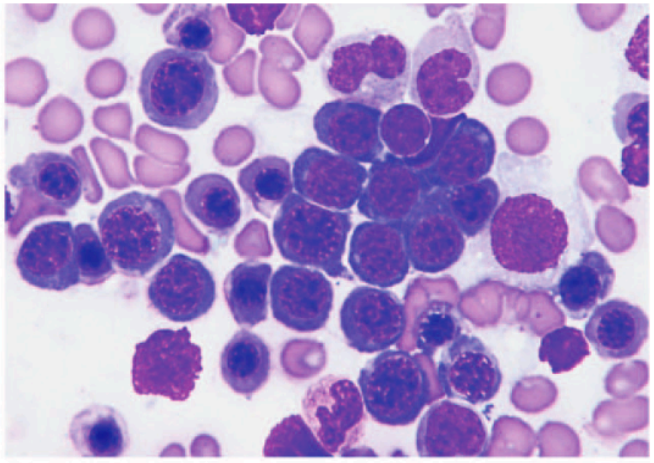
B

BM aspirate:

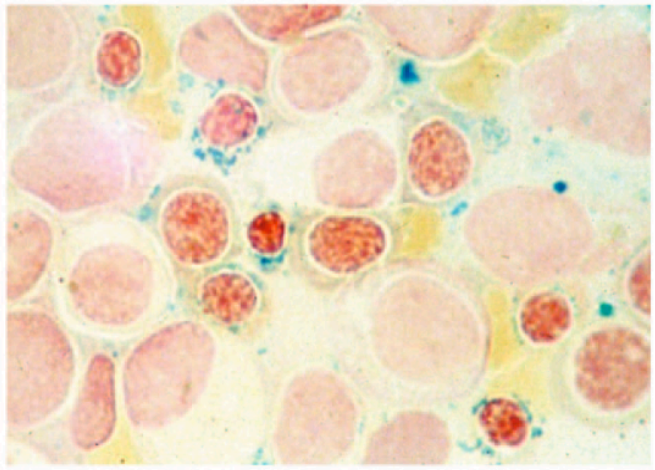
increased clustered megas

BM aspirate:

dysplastic Red blood cells



C



D

BM aspirate:

ringed sideroblast

Cytogenetics: normal
Myeloid mutation panel: ***SF3B1*** & ***JAK2*** **V617F**

From Cazzola *et al*, *Hematology Am Soc Hematol Educ Program*, 2011

MDS/MPN-RS-T (RARS-T)

- SF3B1 mutation in 72% of patients.
  - Prognostic significance (6.9 and 3.3 years for those positive and negative respectively, $p = 0.003$).
- Can be distinguished from RARS by JAK-2 mutation.
  - RARS-T 60% of patients vs 0% in RARS
  - Patients with JAK-2 mutation have better prognosis.
- Two-hit Hypothesis
  - SF3B1 leads to RARS, JAK-2 leads to the -T

Broseus Leukemia 2013

MDS/MPN-U

MDS/MPN-U

Dysplastic feature in 1 type of blood cell
<20% blasts in PB and BM

+

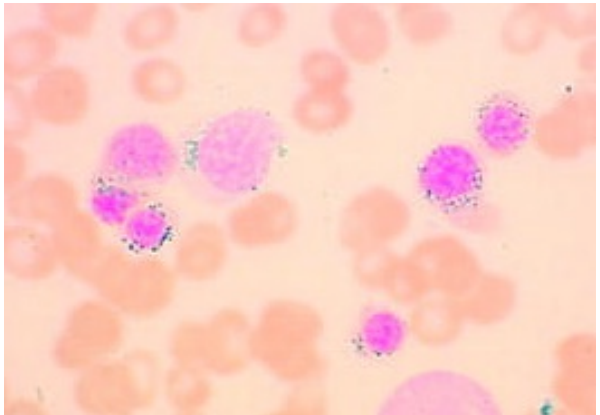
Prominent myeloproliferative features
- Plt > $450x10^9$/L
- WBC >$13x10^9$/L
- ± splenomegaly

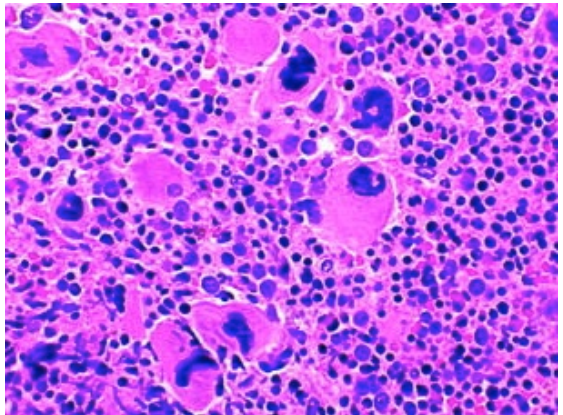
+

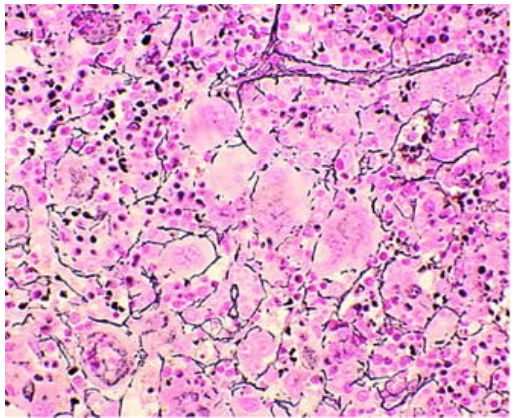
- No history of MPN/MDS
- No cytotoxic or growth factor tx
- No BCR-ABL, PDGFRA, PDGFRB, FGFR1
- No isolated del 5q, t(3;3), or inv 3(q21q26)

OR

de novo disease with mixed MPN and MDS features and not fitting any other category







MD Anderson Study of MDS/MPN-U

- 85 patients with MDS/MPN-U
- Patients with treated with HMA (n = 36), an immunomodulator (n = 13) or stem cell transplant (n = 5)
- Median OS was 12.4 months
- Favorable outcome was associated with
  - Age < 60
  - Thrombocytosis (52.5 months)
  - Lack of circulating blasts
  - < 5% bone marrow blasts.
- MDS-MPN-U patients had worse survival compared with MDS and PMF.
- No treatment regimen proved effective
- Combination therapy with Ruxolitinib and Azacitadine is under investigation.

DiNardo C. Leukemia 2014

The Future of Treatment in MDS/MPN

Goals of Therapy in MDS/MPN

- Cure
- Reduction of symptoms / splenomegaly
- Improvement of blood counts
- Cytogenetic / molecular remission
- Avoidance of disease progression / AML
- Few evidence based recommendations for management other than CMML

TADA Study

- 28 enrolled patients (median age was 66.5 years)
- Treatment: thalidomide, arsenic trioxide, dexamethasone, and ascorbic acid [TADA]
- 15 patients had MDS/MPN-unclassifiable, 8 patients had chronic myelomonocytic leukemia type 1, and 5 patients had PMF.
- With a median follow-up of 5.7 months, 21 patients (75%) completed the 12-week course of therapy, and 6 patients (29%) responded to TADA.
- At 24.1 months (15 evaluable patients), median PFS was 14.4 months, and the median overall survival was 21.4 months.

Bejanyan Cancer 2012

Targeted Therapy Considerations

Mutation	Disease Entity	Therapy	Example
JAK2 V617F	CMML (5-10%) RARS-T (60%), aCML (7%)	JAK inhibitor	Ruxolitinib
CSF3R T618I	CMML (< 5%), aCML (< 10%)	JAK inhibitor	Ruxolitinib
RAS pathway (e.g. *PTPN11, RAS, CBL, NF1*)	CMML (24-37%), aCML (27-54%), MDS-MPN-U (4-16%)	MEK inhibitor	Trametinib
SF3B1	CMML (5-10%), RARS-T (72%), MDS/MPN-U (1%)	TGF-B ligand trap	Luspatercept
Other splicing gene mutations (e.g. *SRSF2*)	CMML (50%), MDS/MPN-U (2%)	Splicing modulator	H3B-8800
IDH 1/2	CMML (< 2%)	IDH 1/2 inhibitor	Enasidinib
CD30+	CMML (30-40%)	Anti-CD30	Brentuximab Vedotin

Studies Open at FHCRC/SCCA

- Randomized study of Guadecitabine in patients who are refractory to azacitabine and decitabine.
  - Open for patients with MDS and CMML.
- H3B-800
  - Will include patients with MDS and CMML.
- Brentuximab Vedotin (SWOG)
  - Will include patients with CMML and systemic mastocytosis.

MDS/MPN: Summary

- MDS/MPN has features common to both MDS and MPN
- Diagnosis is often laboratory and made by a pathologist and though chromosomal and molecular testing.
- The combination of increased WBC and/or platelet counts with anemia can make treatment decisions challenging.
- Hypomethylating agents are commonly employed.
- For younger patients with higher-risk disease and an acceptable co-morbidity index, allogeneic transplant is the preferred treatment.
- Searching for actionable mutations may provide opportunities for targeted therapy.
- Accrual in clinical trials is highly recommended for these rare diseases.

Acknowledgements

- Fred Hutch
  - Joachim Deeg
  - Bart Scott
  - Cecilia Yeung
  - Emily Stevens
- Seattle Cancer Care Alliance
- Patients and Caregivers

Questions??