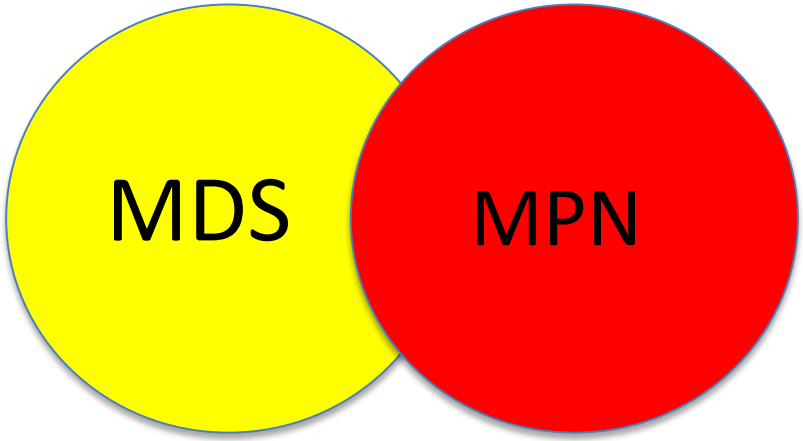
MDS/MPN: What it is and How it Should be Treated?



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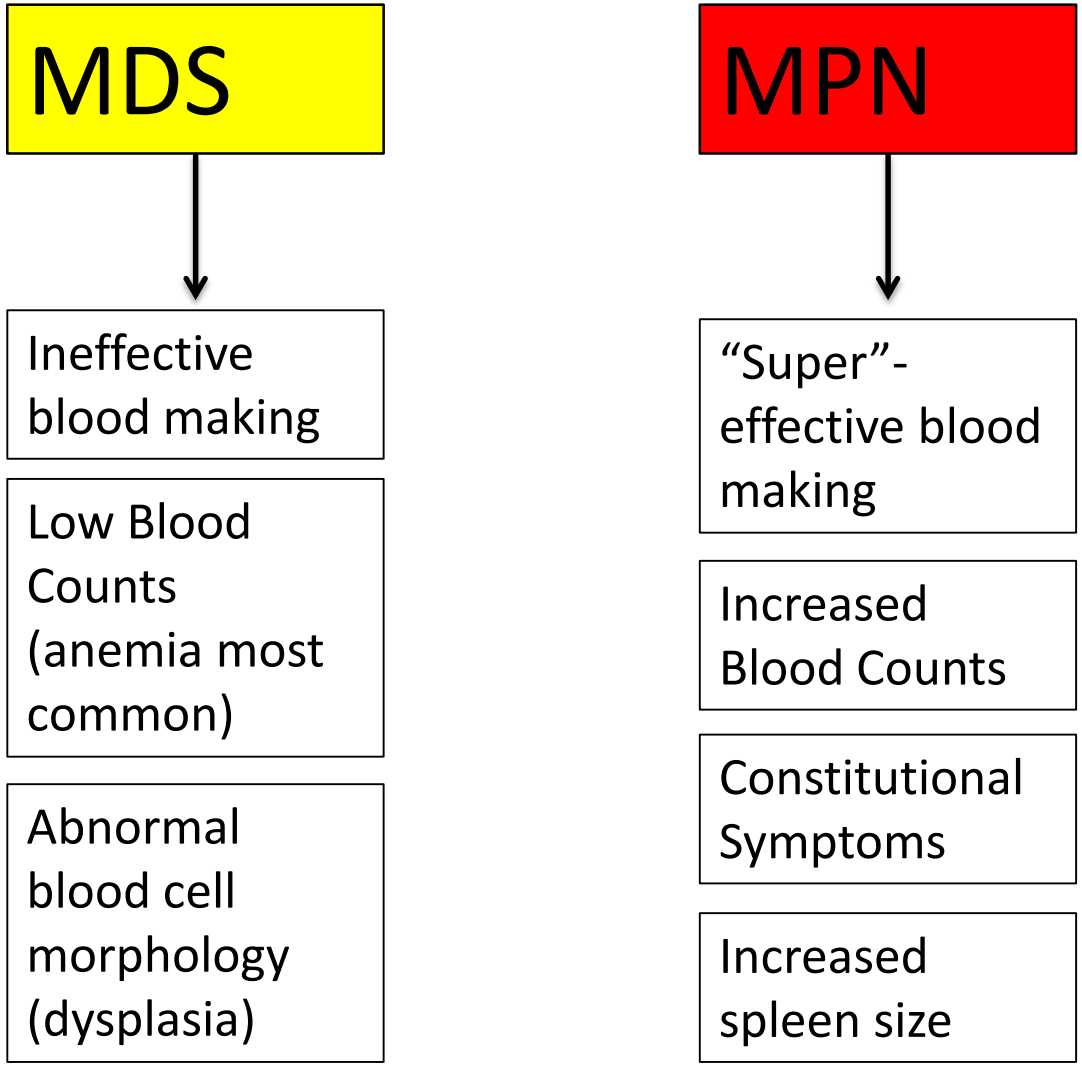
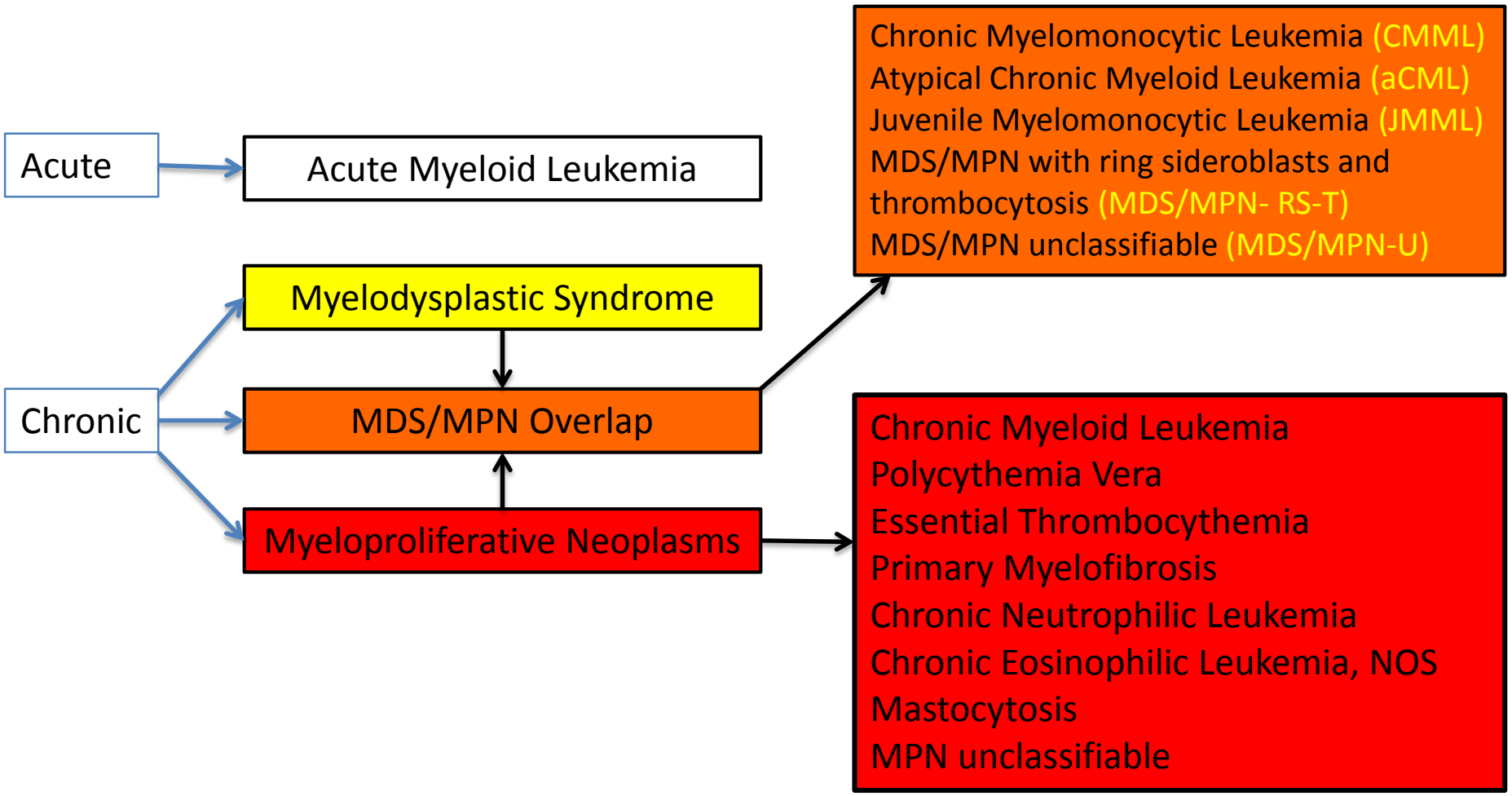
MDS Foundation Patient & Family Forum: August 10, 2019

Features of Myelodysplastic Syndrome (MDS) and Myeloproliferative Neoplasm (MPN)

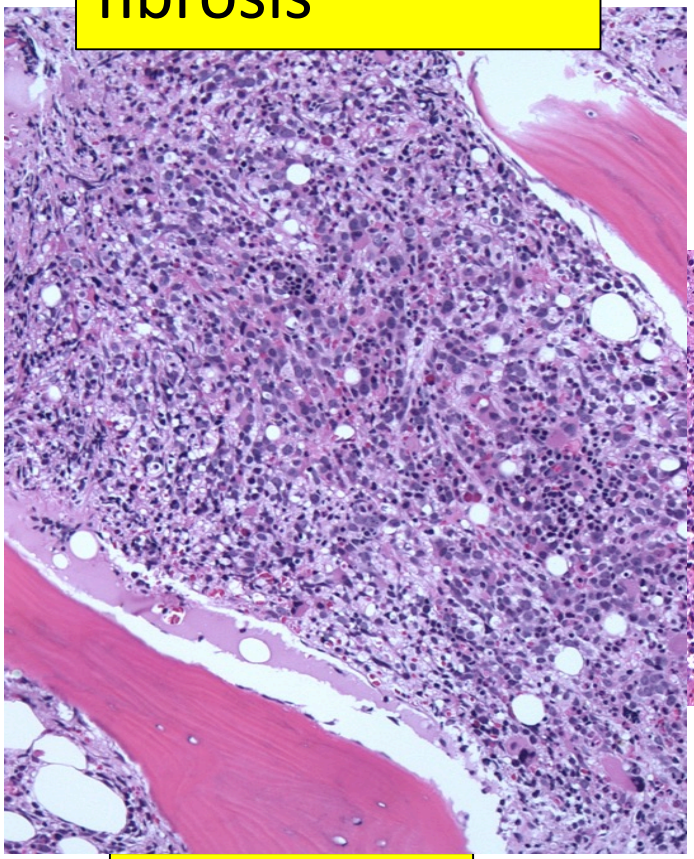


2016 WHO Classification Scheme for Myeloid Neoplasms



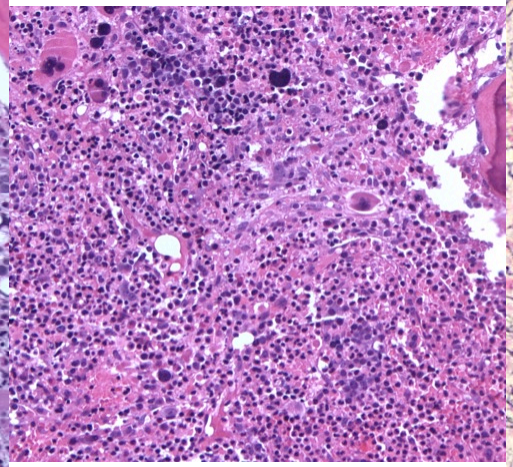
Hematopathologists' Challenge

"Dysplasia with fibrosis"

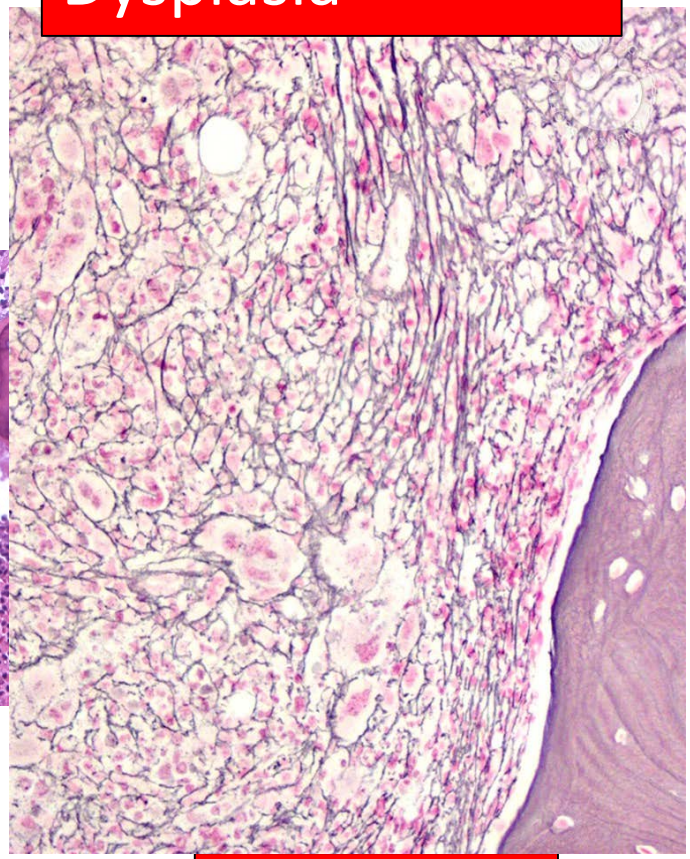


MDS

MDS/MPN



"Fibrotic with Dysplasia "



MPN

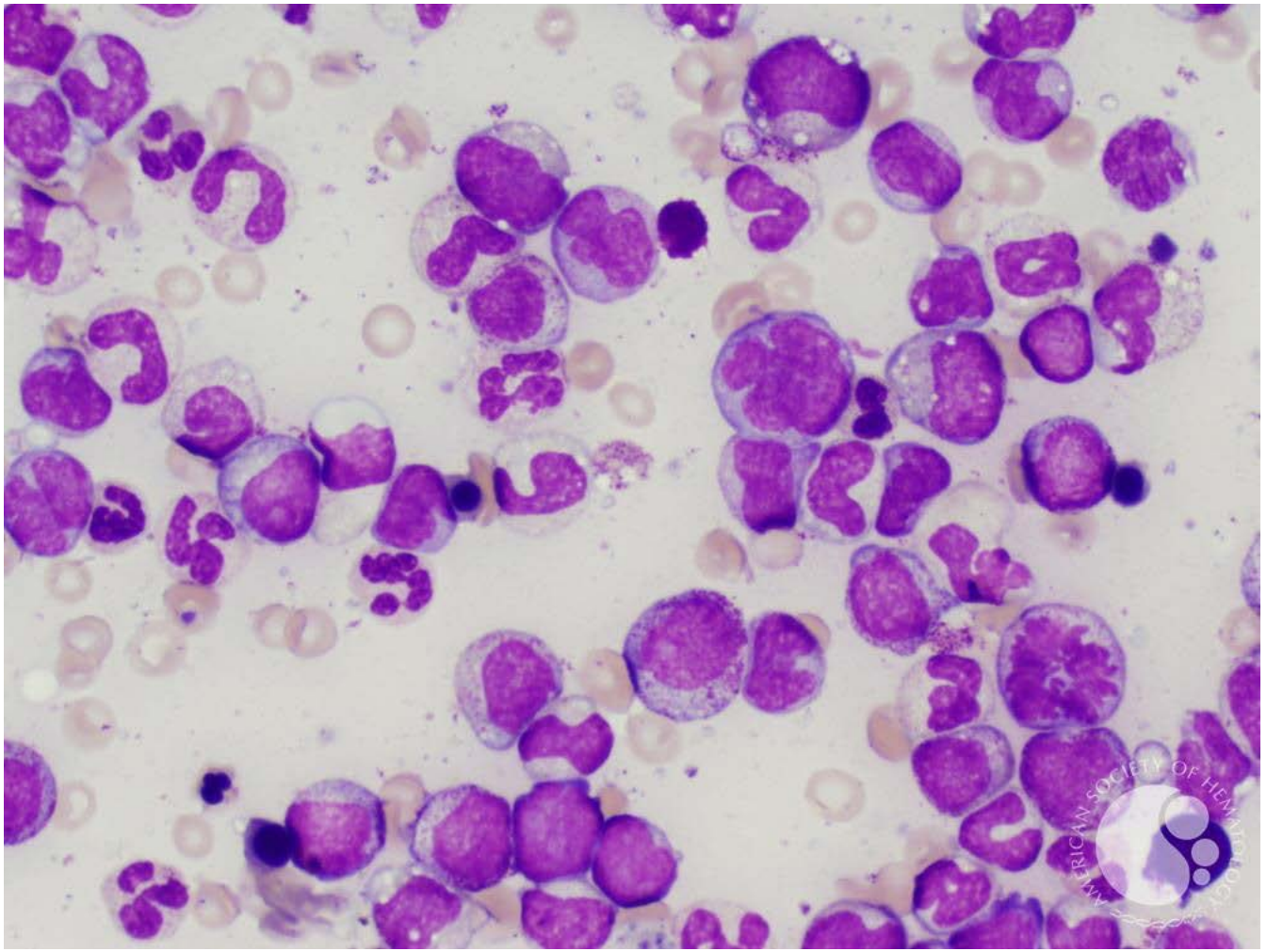
What is MDS/MPN?

- Clonal myeloid neoplasm characterized by presence of both MDS and MPN features.
- MDS with presence of fibrosis does not justify placement in this category.
- Incidence is unknown
- 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)**

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

CMML



The aspirate smears show a myeloid predominance with increased monocytes (16%) and 2% blasts. There are subtle dysplastic features in the neutrophils.

Clinical Symptoms of CMML

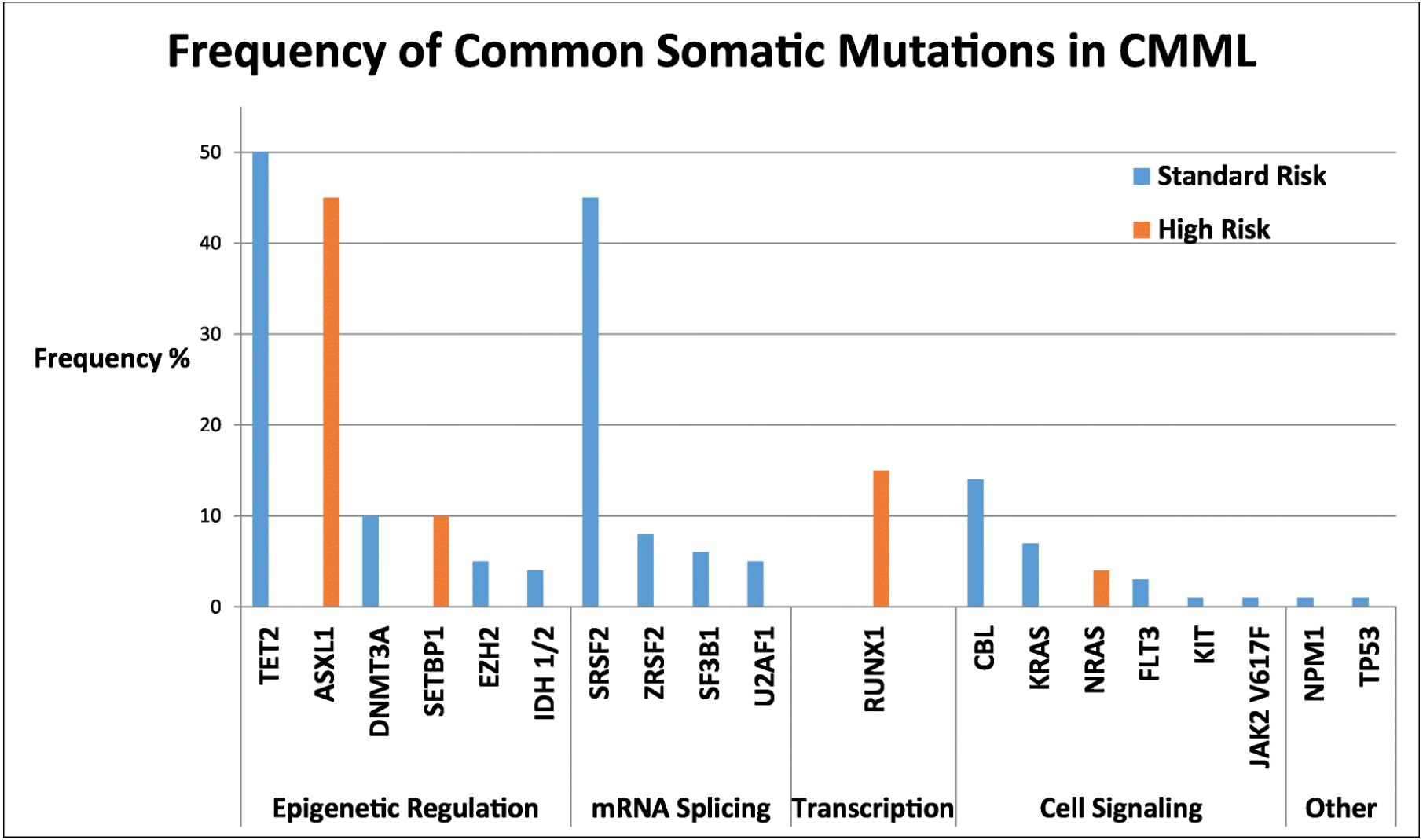
- Fever, fatigue, night sweats, weight loss
- Infections
- Bleeding caused by low platelets
- Large spleen and liver

- Normal or low WBC presents more like MDS
- Elevated WBC presents more like MPN

Incidence and Diagnosis

- Incidence 0.3 per 100,000
- Median age 65-75 years
- Male predominance 3:1
- Typical presentation is monocytosis in the blood.
  - At least 1,000 per mm3 and at least 10% of the WBC on differential
- No BCR/ABL or PDGFR rearrangement.
- Fewer than 20% blasts in the blood or bone marrow
- Dysplasia in ≥ 1 cell line

Molecular Pathology



Prognostic Factors in CMML

- Blood and marrow blast count
  - CMML- 0-blood < 2%;marrow < 5%
  - CMML-1- blood 2-4%; marrow 5-9%
  - CMML-2-blood 5-9%; marrow 10-19%
- WBC Count
  - MDS CMML ≤ 13,000
  - MF CMML > 13,000
- Low Hemoglobin (< 10 or transfusion dependent)
- Age
- Platelets < 100
- Genetic risk group based on cytogenetics and mutations.

Mayo, GFMScore, CPSS, Molecular Mayo

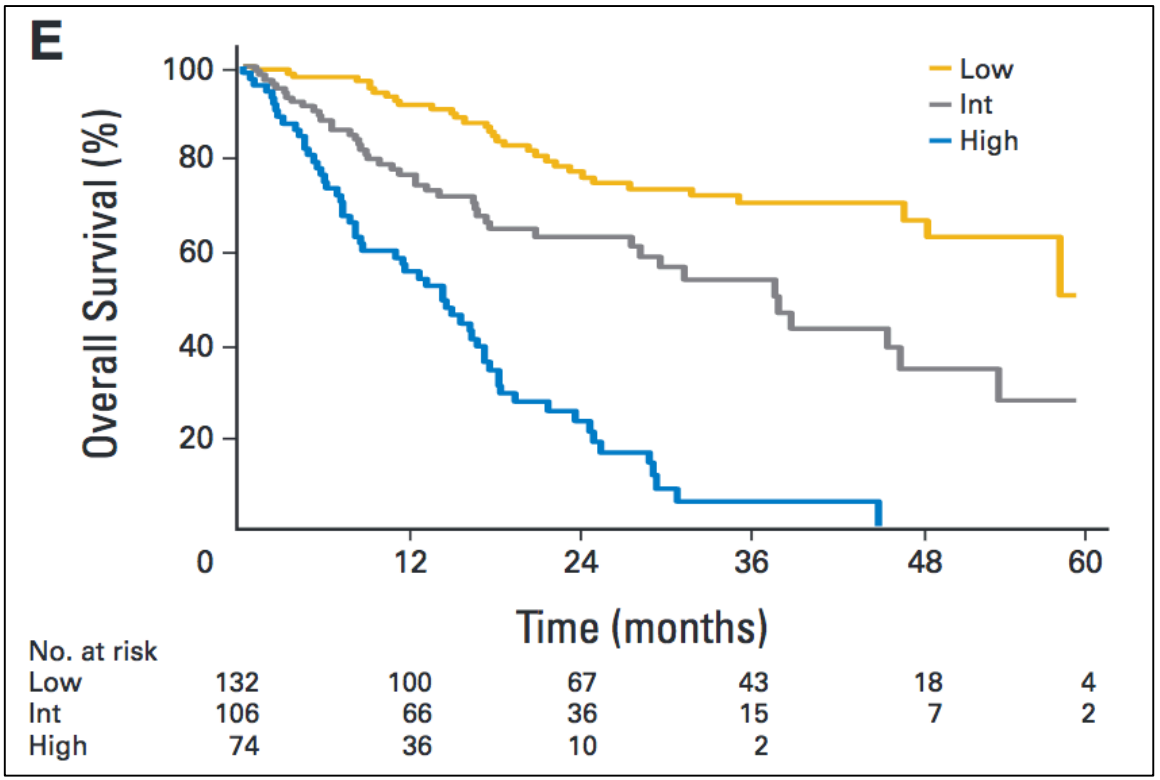
CMML Prognostic Model: Bone Marrow Blast % and WBC Count

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

CMML Prognostic Scoring System



	Absence	Presence
Leucocytosis (>15)	0	3
Age (>65)	0	2
Anemia	0	2
Thrombocytopenia (<100)	0	2
ASXL1 mutation	0	2

Low < 4
Intermediate 4-8
High >8

Itsykson *et al*, *J Clin Oncol*, 2013

Treatment for CMML

- Low risk patients
  - Monitoring or symptom management
  - ESAs for patients with cytopenias
  - Hydrea or etoposide for high WBC count or splenomegaly (60% response rate)
- High risk and young or fit patients
  - Multiagent chemotherapy for leukemic transformation
  - Hypomethylating agents (may not improve survival over supportive care)
  - Allogeneic Transplantation

Phase I/II Trials of Hypomethylating Therapy in Patients with CMML

- Overall response rate: 25-70% (usually ~30-40%)[1]
- Complete remission rate: 10-58%
- Overall Survival (OS): 12-37 months
- Prognostic factors for OS 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 for CMML

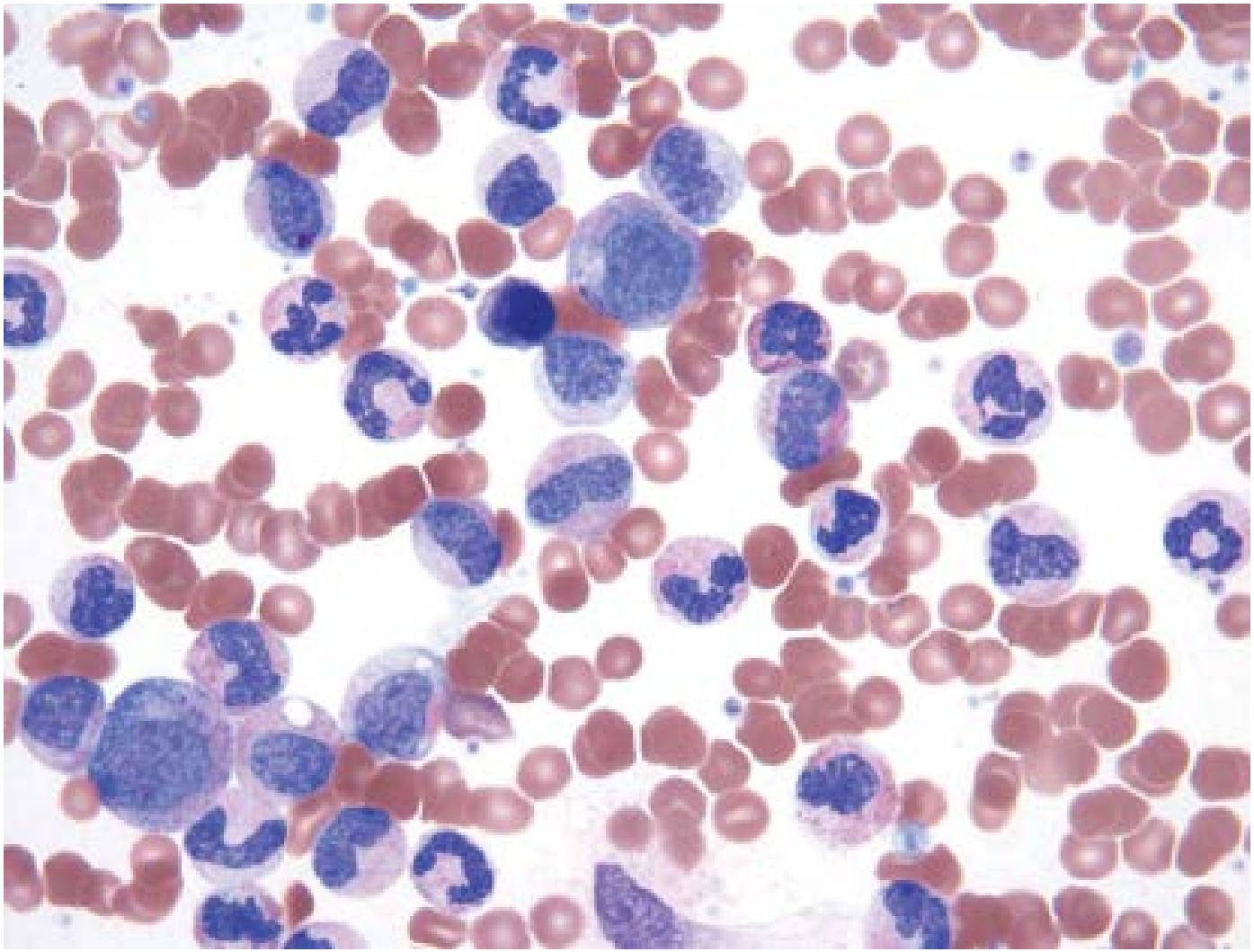
- No randomized trials
- Increasing use of reduced intensity conditioning
  - Other donor sources: haploidentical; double umbilical cord units
- CMML at Fred Hutch (n = 129)[1]
  - 10-yr overall and relapse-free survival: 38% and 28%, respectively
  - poor-risk molecular and cytogenetics as well as minimal residual disease at the time of transplant were associated with 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] Woo J, Haematologica 2019
[2] Symeonidis *et al*, Br J Haematol, 2015

Clinical Trials

- Guadacitabine (just completed at our center)
- Oral decitabine with the cytidine deaminase inhibitor cedazuridine
- Lenalinomide + HMA (68% response rate)
- Ruxolitinib (35% response rate)
- Tipifarnib (Farnesyl Transferase Inhibitor)
- CD123 Antibody (targets CMML cells)

Atypical CML



"Dysgranulopoiesis"

Clinical Presentation and Diagnosis

- Adults with male predominance
- Organomegaly
- Elevated WBC, neutrophilia but *no basophilia (CML) or monocytosis (CMML)*
- Hallmark is severe “dysgranulopoiesis”
- Hypercellular BM with granulocytic proliferation and dysplasia.
- No PDGFR rearrangement
- BCR/ABL negative

Schwartz L Blood Reviews January 2019

Molecular Pathogenesis

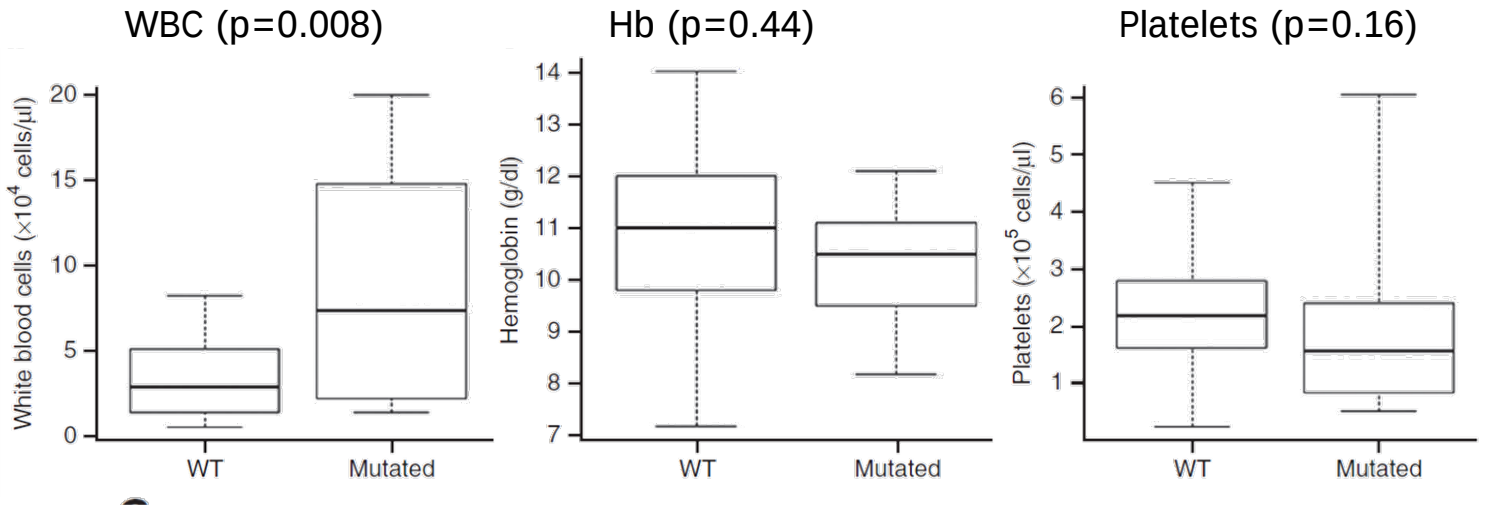
- Chromosomal abnormalities in 20-88%
  - Aneuploidy in 33%-most common trisomy 8, del20q
- Somatic gene mutations
  - SETBP1 mutation in 18-33% (worse prognosis)
    - Coexists with ASXL1 in 48-65%
  - CSF3R mutations in 10-40%
  - KRAS and NRAS in 10-30%
  - ETNK1 mutations in 9%

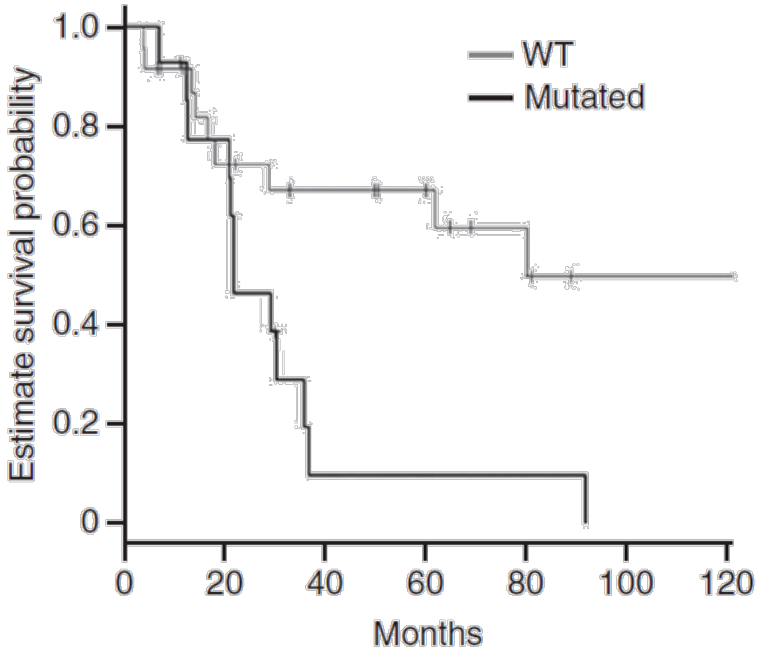
Atypical CML: Disease Course

- Median age 70
- Male predominance
- 1-2 cases for every 100 cases of BCR/ABL positive CML
- Overall median survival: 14 to 30 months.[2-4]
- Transformation to AML in 40% at a median time from diagnosis of 18 months[1]
- Predictors of shorter survival:
  - Older age (>65 years)
  - Female gender
  - WBC count (>50x10^9/L)
  - Hb < 10
  - > 10% immature circulating cells.
  - SET BP1 mutation

[1] Breccia *et al*, *Haematologica,* 2006
[2] Kurzrock *et al*, *J Clin Oncol,* 2001
[3] Martiat *et al*, *Blood*, 1991
[4] Hernandez *et al*, *Ann Oncol,* 2000

SETBP1 Mutation in Atypical CML





SETBP1- = 77 months
SETBP1+ = 22 months

p=0.01, HR=2,27

Piazza R. *et al*, Nat Genetics 2013

Treatment Options

- Symptomatic control
  - Hydrea, INF-alpha: complete and partial responses with duration of months
  - Splenectomy not recommended
  - ESAs-poor response
- HMAs-CRs shown in limited numbers of patients
- Clinical trials
  - Ruxolitinib (JAK inhibitor) in patients with CSF3R and JAK2 mutations
  - Dasatinib (SRC kinase inhibitor) for patients with CSF3R mutations
  - Trametinib (MEK inhibitor) in patients with CSF3R mutations

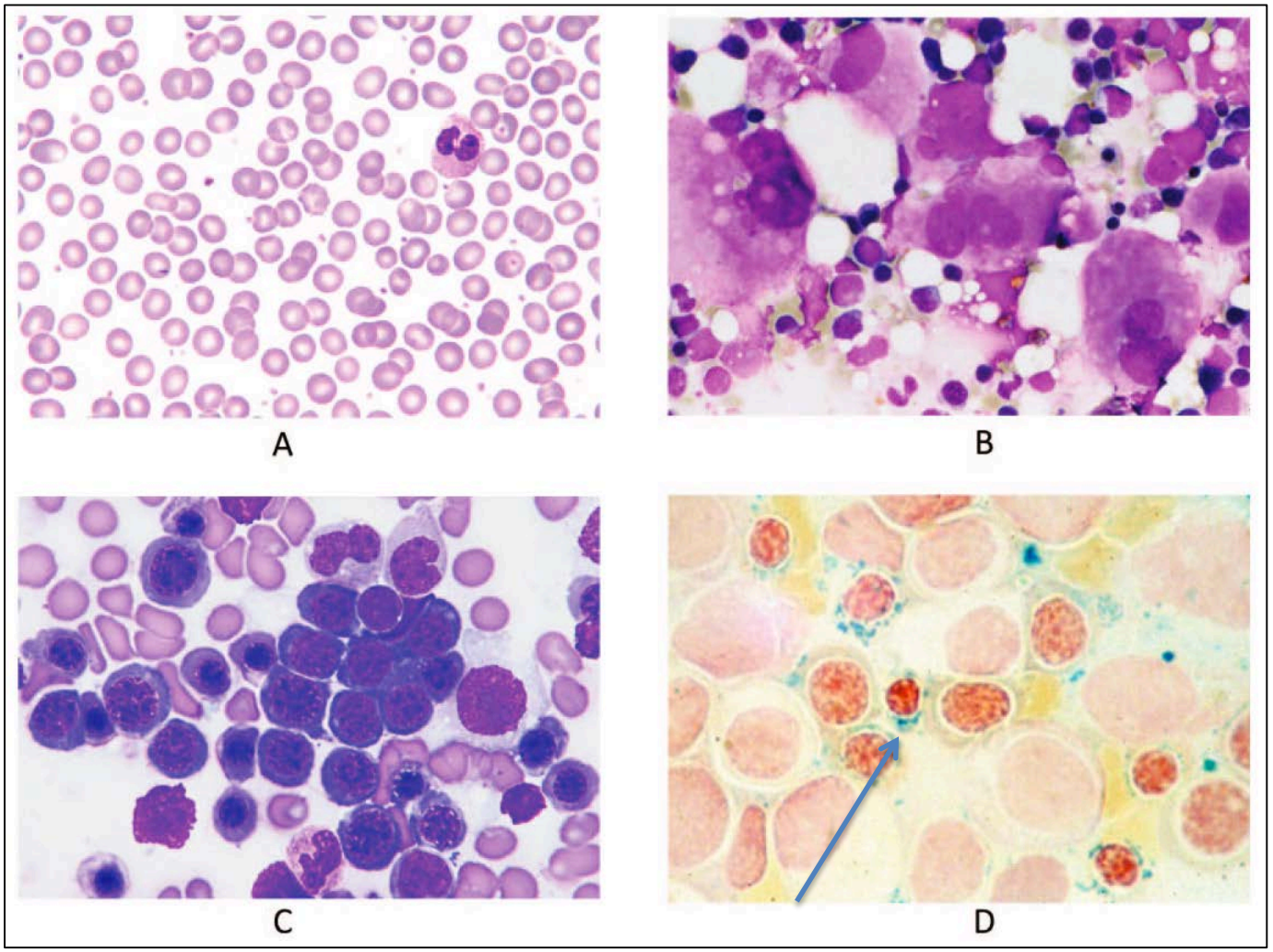
Schwartz L Blood Reviews January 2019

Hematopoietic stem cell transplant in Atypical CML

- 21 patients with aCML[1]
  - 17 alive at 5 years post transplant with median survival 46.8 months
- 42 patients with aCML reported by EMBT[2]
  - OS of 51% and RFS 36% at 5 years
  - Offer at time of diagnosis in young fit patients

1. Koldehoff M Int J LabHematol 2012
2. Onida F BJH 2017

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



RS usually signifies ineffective erythropoiesis and mitochondrial iron overload.

Clinical Presentation

- Median age 71-75 years
- Venous Thrombosis (3.9/100 patient years)
  - SF3B1 mutation patients more likely to have thrombosis (20%)
- Anemia
- Bleeding (Von Willebrands Disease)
- Vasomotor symptoms:
  - Migraine headaches
  - Palpitations
  - Paresthesias
  - Atypical chest pain

Patnaik MM Am Journal Hem April 2019

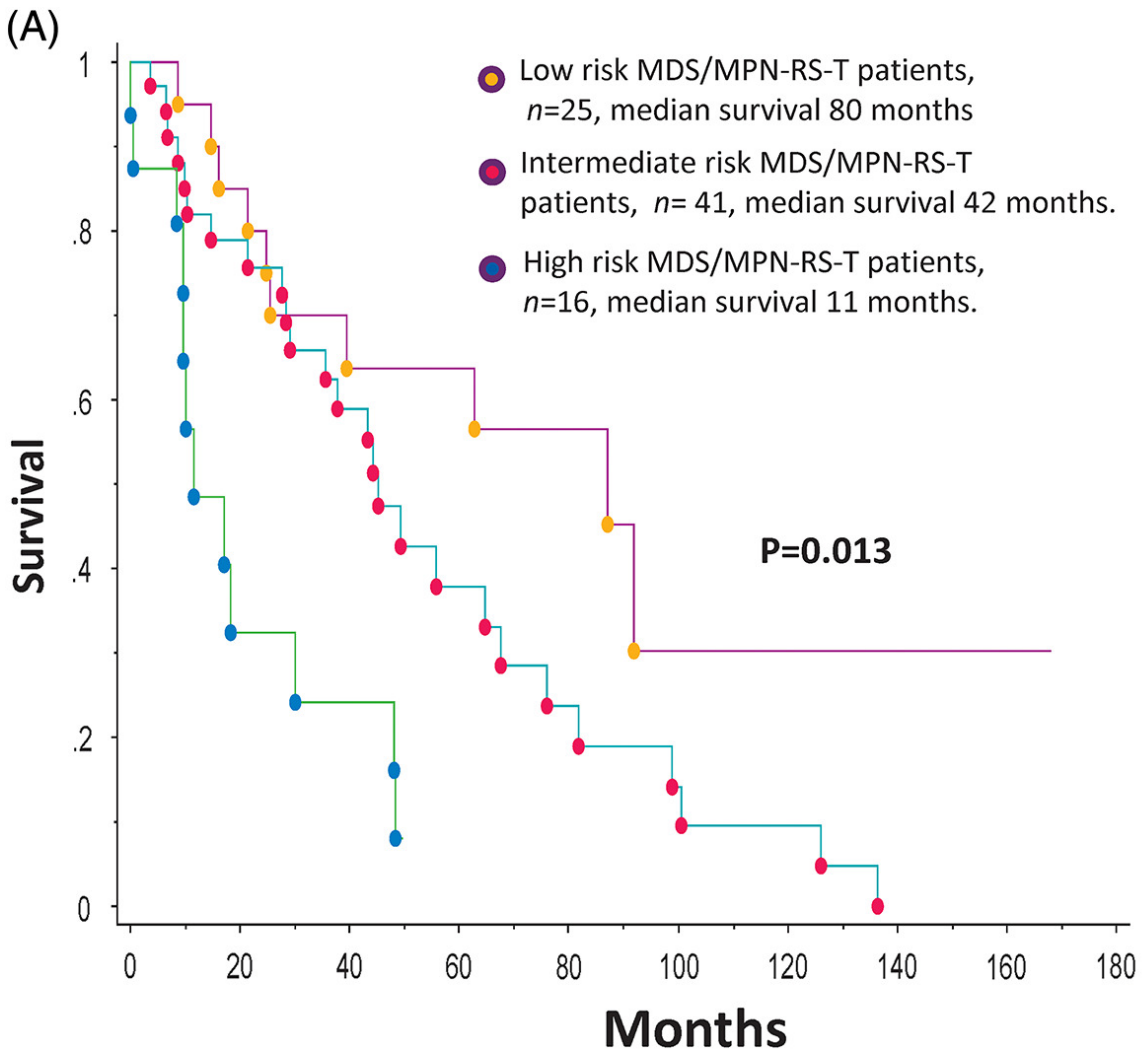
Diagnostic Critiera

- Features of MDS-RS-SLD + sustained elevated platelets (> 450,000) + proliferation of large atypical megakaryocytes
- No history of MDS or MPN except MDS-RS
- No BCR-ABL or PDGFR or PCM1-JAK2
- No t(3,3), inv3 or del5q
- SF3B1 mutation with > 15% RS

Patnaik MM Am Journal Hem April 2019

Molecular Mutations

- 80% have normal cytogenetics
- In Mayo clinic study 94% of patients had at least one mutation.
- SF3B1 mutation in 85% of patients
  - Prognostic significance (6.9 and 3.3 years for those positive and negative respectively, *P*=0.003).
- JAK-2 mutation (33-50%)
- ASXL1 in 20-29% (poor prognosis)
- DNMT3A in 13-15%
- SETBP1 10-13% (poor prognosis)
- TET2 10-25%



- 2 points for abnormal karyotype
- 1 point for ASXL1 or SETBP1
- 1 point for Hb< 10

- Low=0 points (80 months)
- Intermediate = 1 point (42 months)
- High = 2 or more points (11 months)

Patnaik MM Am Journal Hem 2016

Treatment for MDS/MPN-RS-T

- Management is similar to low risk MDS
- ESA and supportive care early on
- Case reports of lenolinomide to decrease anemia
- ASA for thrombosis prevention
- Cytoreductive therapy controversial due to anemia
  - Hydrea
  - Lenolinomide
  - Interferon
  - Busulfan
- Allogeneic Transplant for refractory cytopenias or progressive disease

MDS/MPN-U

MDS/MPN-U

- Dysplastic Feature in at least 1 type of blood cell and <20% blasts in the peripheral blood and marrow
- Prominent myeloproliferative features
  - Plt > 450,000
  - WBC > 13,000
  - +/- splenomegally
- No history of MDS/MPN
- No Cytotoxic or growth factor treatment
- No BCR-ABL or PDGFR
- No isolated del 5q-, t (3,3) or inversion 3 OR
- Not fitting any other categories

Clinical Features of MDS/MPN-U

- Median age 70 yrs
- 72% male
- 35% have splenomegaly
- Majority of patients have diploid cytogenetics (49%) or trisomy 8
- 12% have complex karyotype
- Approximately 25% have JAK-2 mutation

DiNardo C. Leukemia 2014

MD Anderson Study of MDS/MPN-U

- Median OS was 12.4 months (21 months from diagnosis)
- Favorable outcome was associated with
  - Age < 60
  - Thrombocytosis (52.5 months)
  - Lack of circulating blasts
  - < 5% bone marrow blasts.
- MDS-IPSS score provided significant prognostic information while the MF DIPSS did not
- MDS-MPN-U patients had worse survival compared with MDS and PMF.

DiNardo C. Leukemia 2014

Mutational Landscape of MDS/MPNU

- ASXL1, TET2 (21%)
- JAK2 (19%)
- SRSF2 (15%)
- EZH2 (14%)
- U2AF1, RUNX 1, SETBP1 (11%)
- At least 1 mutation was associated with worse OS (11.8 months vs 28.6 months)
- ASXL1/SRSF2 combo was more likely to develop AML

Bose P Letter to the Editor Blood 2018

Treatment

- No standard treatment regimen
- No treatment regimen proven effective
- Combination therapy with Ruxolitinib and Azacitadine is under investigation.

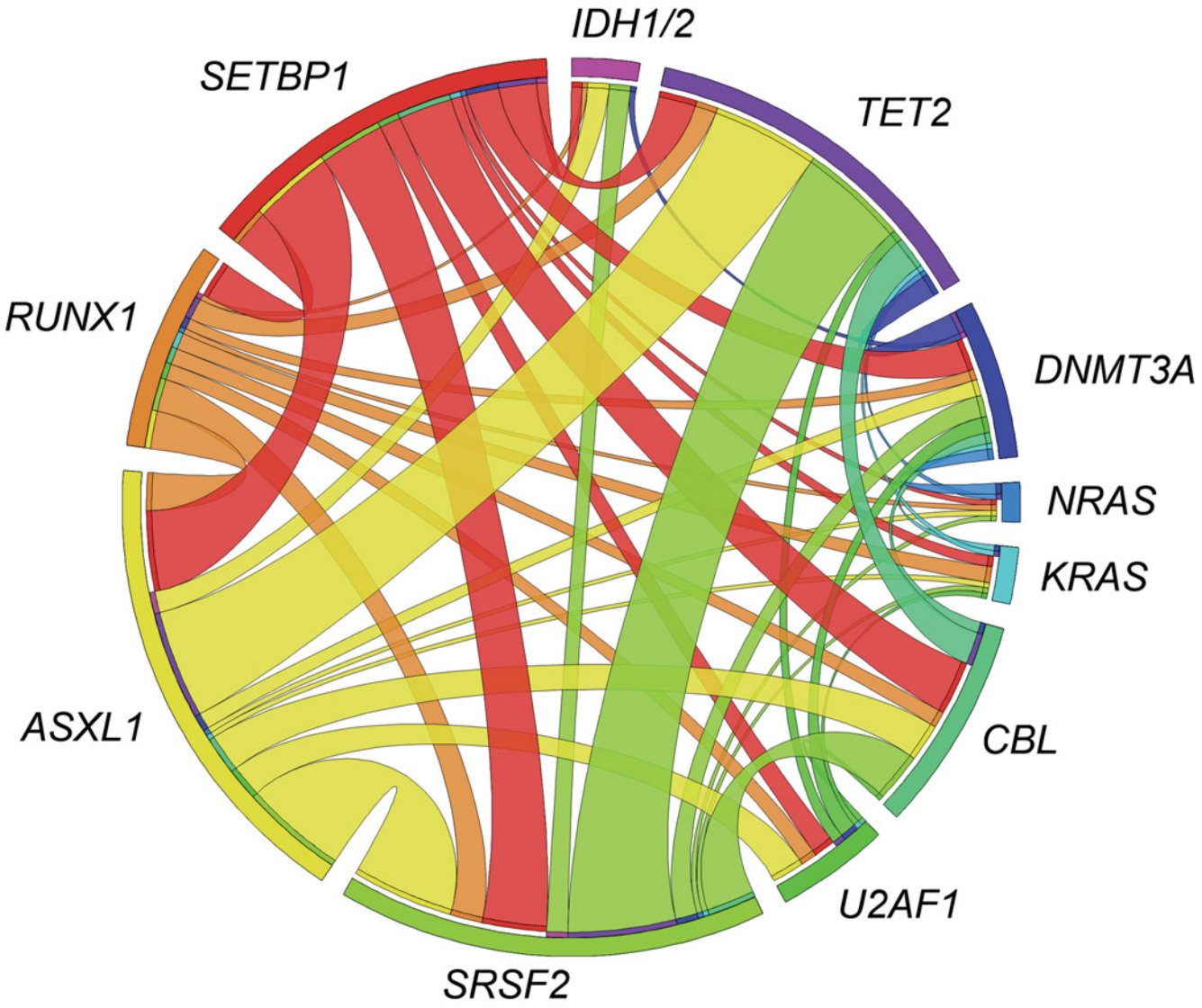
MDS/MPN: Summary

- MDS/MPN has features common to both MDS and MPN
- Diagnosis is often 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
- Seattle Cancer Care Alliance
- Patients and Caregivers

Questions??


IDH1/2
SETBP1
TET2
RUNX1
DNMT3A
NRAS
KRAS
ASXL1
CBL
U2AF1
SRSF2