Myelodysplastic Syndrome & Myeloproliferative Neoplasms
Introductory Lecture

MDS & MPN

MDS

dysfunctional maturation

of the bone marrow

UNDER-production

of one or more cell line

MPN

dysfunctional activation

of the bone marrow

OVER-production

of one or more cell line

MDS & MPN

MDS

- MDS with single lineage dysplasia
- MDS with multi lineage dysplasia
- MDS with ring sideroblasts
- MDS with excess blasts
- MDS with del(5q)
- Unclassifiable MDS

* Diagnostic criteria in flux based on WHO 2022 and ICC competing delineations.

MPN

Common

- CML
- Polycythemia Vera
- Essential Thrombocytosis
- Primary Myelofibrosis

Rare

- Chronic Neutrophilic Leukemia
- Chronic Eosinophilic Leukemia
- Mast Cell Disease
- Unclassifiable MPN

Myelodysplastic Syndrome
MDS

MDS Pathology

Pathology

dysfunctional maturation of the bone marrow

UNDER-production of one or more cell line

* Despite peripheral cytopenias, BM often hypercellular

Risk Factors

RISK FACTORS
Age (Avg 60s)
Gender (Male)
Chemotherapy exposure Radiation therapy exposure

Sub-Types

- MDS with single lineage dysplasia
- MDS with multi lineage dysplasia
- MDS with ring sideroblasts
- MDS with excess blasts
- MDS with del(5q)
- Unclassifiable MDS

* All with < 20 % blasts (> 20% = AML)

MDS Risk Scoring

Risk Group	R-IPSS Score	OS (years)
Very Low	< 1.5	8.9
Low	1.5 - 3	5.3
Intermediate	3 - 4.5	3.0
High	4.5 - 6	1.6
Very High	> 6	0.8

* IPSS-M (mutations) is a new risk scoring system available

Revised IPSS (International Prognostic Scoring System)		
BMB Blasts	0	< 2%
	1	2-5%
	2	5-10%
	3	> 10%
Cytogenetics	0	very good (del11q)
	1	good (del5q, del12p, del20q)
	2	intermediate (del7q, trisomy 8, inv17q, +19)
	3	poor (inv3, del3q, -7)
	4	very poor (complex)
Hemoglobin 	0	> 10
	1	8-10
	2	< 8
Platelets 	0	> 100
	0.5	50-100
	1	< 50
ANC 	0	> 800
	1	< 800

MDS Treatment

WHEN TO TREAT: Symptomatic cytopenias not managed by growth factor support, recurrent Infections

5q Disease

Lenalidomide
* Low/Intermediate IPSS

Low IPSS (non 5q)

EPO (if EPO < 500) +/- GCSF

Hypomethylating Agent (HMA):
Decitabine
Azacitidine

ATG + Cyclosporine

Luspatercept
* In SF3B1+ with ringed sideroblasts

Lenalidomide
*Can also be used in non-5q MDS

Clinical Trial

Intermediate/High IPSS (non 5q)

Transplant Candidate =
HMA
AlloSCT

Not Transplant Candidate =
HMA

Myeloproliferative Neoplasms
MPN

MPN Types

MPN

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- Polycythemia Vera
- Essential Thrombocytosis
- Primary Myelofibrosis
- Chronic Neutrophilic Leukemia
- Chronic Eosinophilic Leukemia
- Mast Cell Disease
- Unclassifiable MPN

MAJOR TYPES

CML

Polycythemia Vera

Essential Thrombocytosis

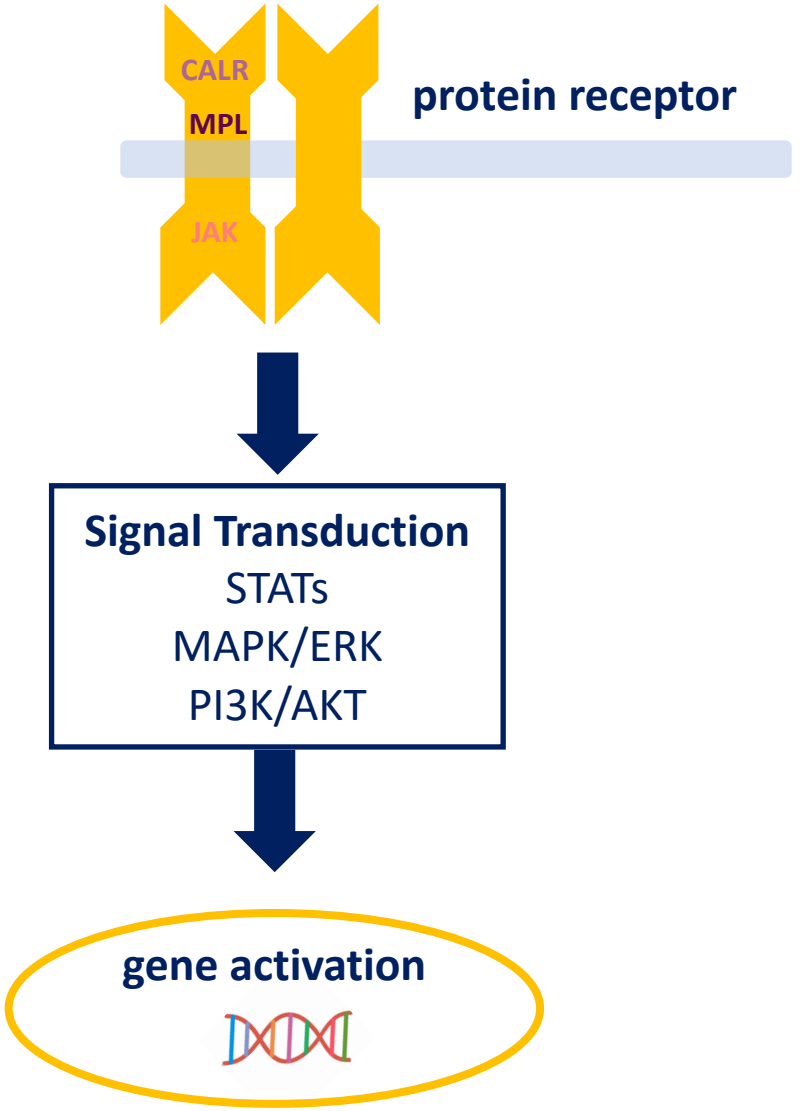
Primary Myelofibrosis

MPN Major Types

CML		Over-production WBCs
Polycythemia Vera		Over-production RBCs
Essential Thrombocytosis		Over-production of Plts
Primary Myelofibrosis		Burned out BM

MPN Genetics

Three major mutations in MPN: JAK2, CALR, MPL



MPN Genetics

Three major mutations in MPN: JAK2, CALR, MPL

JAK2

- Intracellular signal transduction
- Most common mutation in MPN
- 90% PV
- 50-60% ET/PMF

CALR

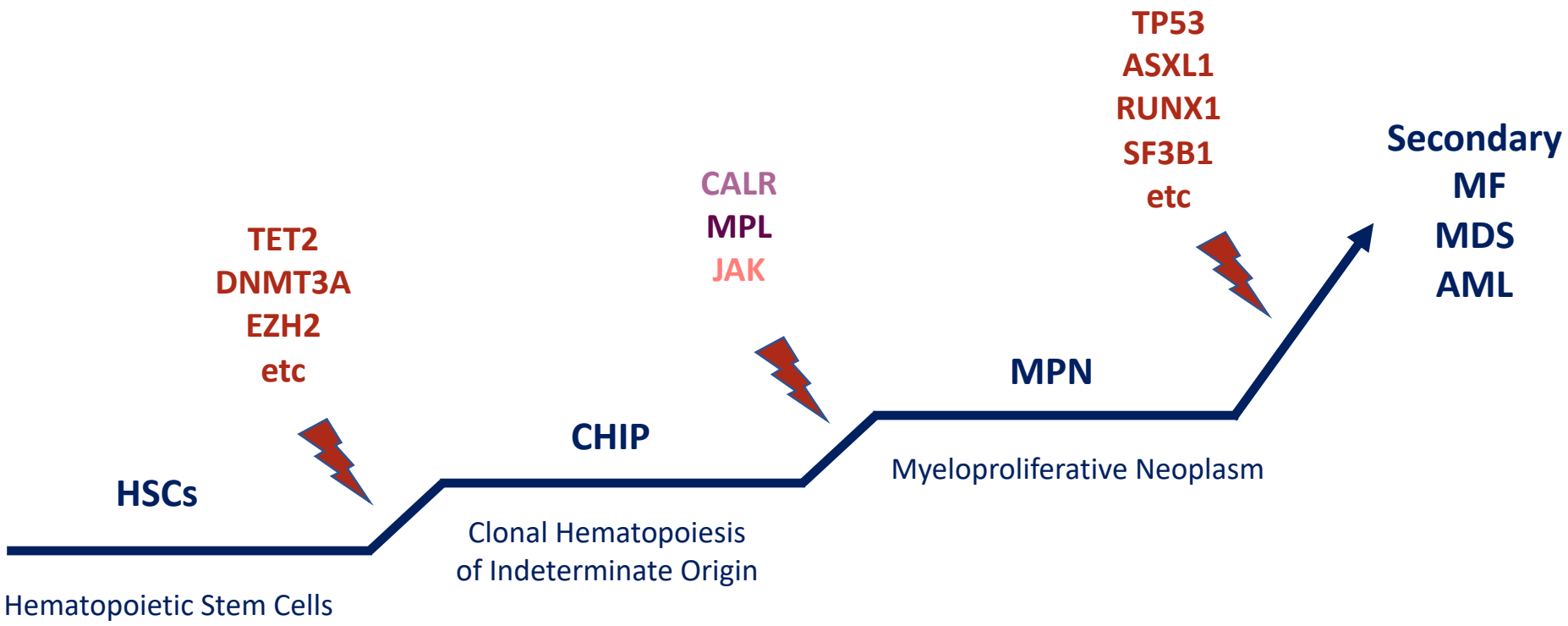
- Ca binding protein
- Rare in PV
- 70% of ET/PMF [w/o ΔJAK2]

MPL

- Encodes thrombopoietin receptor (TPO-R)

MPN Progression

MPN is part of a disease spectrum



MPN Major Types

Ph+ MPNs

CML

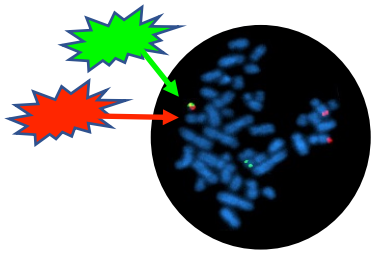
Ph- MPNs

Polycythemia Vera

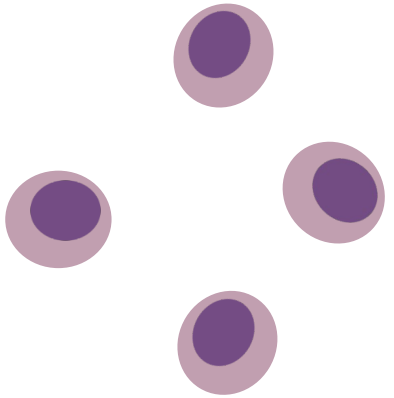
Essential Thrombocytosis

Primary Myelofibrosis

CML



Over-production WBCs



BCR-ABL fusion gene
t(9,22)

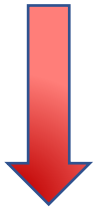
Peripheral smear with left shift: increased immature WBCs
= myeloblasts, promyelocytes, myelocytes, metamyelocytes

CML

CML = Overproduction of WBCs	
LAB HYPERPLASIA	**Leukocytosis : often 20-700K** **Left shift to immature cells** * Sometimes thrombocytosis
GENETIC MUTATION	**BCR-ABL** **t(9;22)**
BONE MARROW BIOPSY	**Hypercellular**

CML

CML Phases	
Chronic	
Accelerated	Increasing WBC Basophils > 20% Myeloblasts/promyelocytes > 30% Peripheral/BMB blasts 10-19% Plts > 1 million or < 100K Splenomegaly
Blast	> 20 % BMB blasts



worse prognosis

CML

First Generation TKI

Imatinib	QTC Rash Diarrhea Muscle cramps Fluid Retention

* Usually only used in chronic phase

Second Generation TKI

Dasatinib *** Penetrates CNS**	QTC Pleural Effusion Pericardial Effusion Pulmonary HTN Thrombocytopenia
Nilotinib	QTC Pancreatitis Hyperglycemia Hyperlipidemia GI/Liver toxicity
Bosutinib	Rash Diarrhea GI/Liver toxicity

Third Generation TKI

Ponatinib	QTC Thrombosis CHF Liver toxicity Pancreatitis Fluid retention
Asciminib	URIs Rash Diarrhea GI Toxicity

* Used for T315I mutation or 2nd line

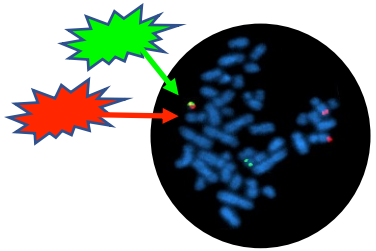
*** These TKIs also used in Ph+ ALL**

**** Different doses used in chronic vs. accelerated phase CML**

CML

CML Phases	Treatment by Phase
Chronic	1st TKI 2nd TKI 3rd TKI
Accelerated	2nd TKI 3rd TKI Evaluate for SCT
Blast	De Novo Blast: Trial TKI Develops on TKI: Chemotherapy + TKI (check for resistance mutations) Evaluate for SCT

PCR Monitoring: Check BCR-ABL PCR Q3 months



3 months:

PCR > 10% check for resistance mutations

6 months:

PCR > 10% = treatment failure, switch TKI

12 months:

PCR > 1% = treatment failure, switch TKI & consider ASCT

Polycythemia Vera

PV = Overproduction of RBCS	
LAB HYPERPLASIA Major Criteria	**Hb > 16** * Sometimes Thrombocytosis
GENETIC MUTATION Major Criteria	**JAK2 (90%)** V617F or exon 12
BONE MARROW BIOPSY Major Criteria	**Hypercellular**
Minor Criteria	**Low EPO**
Symptoms/Complications	Splenomegaly Thrombosis Acquired VWD

Polycythemia Vera

Low Risk Treatments

Aspirin 81 mg

Phlebotomy
goal Hct < 45

High Risk Features

- **Age > 60**
- **Thromboembolism**

High Risk Treatments

Aspirin 81 mg

Phlebotomy
goal Hct < 45

Front Line

Hydroxyurea
goal Hct <45

IFN alpha

Second Line

Ruxolitinib (Jakafi)
JAK1/2 inhibitor
* need to taper off

Essential Thrombocytosis

ET = Overproduction of Plts	
LAB HYPERPLASIA Major Criteria	**Plts > 450**
GENETIC MUTATION Major Criteria	**JAK2 (60%)** **CALR (20%)** **MPL (3%)**
BONE MARROW BIOPSY Major Criteria	**Proliferation/Atypia of Megakaryocytes**
Minor Criteria	**Rule out reactive thrombocytosis**
Symptoms/Complications	Vasomotor: HA, palpitations, livedo reticularis, erythromelalgia Splenomegaly Thrombosis Acquired VWD

Essential Thrombocytosis

Low Risk Treatments

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High Risk Features

- Age > 60
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High Risk Treatments

Aspirin 81 mg

Front Line

Hydroxyurea

IFN alpha

Second Line

Anagrelide
* Inhibits terminal differentiation megakaryocytes

Primary Myelofibrosis

CAUSES

1. **PRIMARY MF**
2. **SECONDARY MF (post ET/PV)**

MF = Bone Marrow Fibrosis = Burned out BM	
LAB HYPOPLASIA	**Pancytopenia** Tear drops
GENETIC MUTATION	**JAK2, CALR, MPL**
BONE MARROW BIOPSY	**BM Fibrosis** Proliferation/Atypia of Megakaryocytes
Extramedullary Hematopoiesis (Liver and Spleen)	**HSM** Tear drops

Primary Myelofibrosis

PMF Treatment Paradigm

Low Risk + Asymptomatic
Observe

Low Risk + Symptomatic
Treat
- Growth factors
- Cytoreduction
- Ruxolitinib (Jakafi)

Intermediate/High Risk
Evaluate for HSCT

*** Many risk scoring systems**
Ex: MIPSS70+ v2.0

MF + Anemia

EPO

Danazol

Lenalidomide +/- Steroids

MF + Thrombocytopenia

Pacritinib
Plts <50

MF + Splenomegaly

Splenectomy

Ruxolitinib (Jakafi)
* Even if no JAK2 mutation
* Can cause thrombocytopenia

Fedratinib
* Semi-selective JAK2 inhibitor

Hydroxyurea

Chronic Myelomonocytic Leukemia
CMML

CMML Pathology

CMML is an overlap syndrome between MDS and MPN

MDS Features

Cell-line dysplasia
Anemia
Thrombocytopenia

MPN features

Cell-line hyperplasia
Leukocytosis
Monocytosis
Splenomegaly

CMML Pathology

Diagnosis:

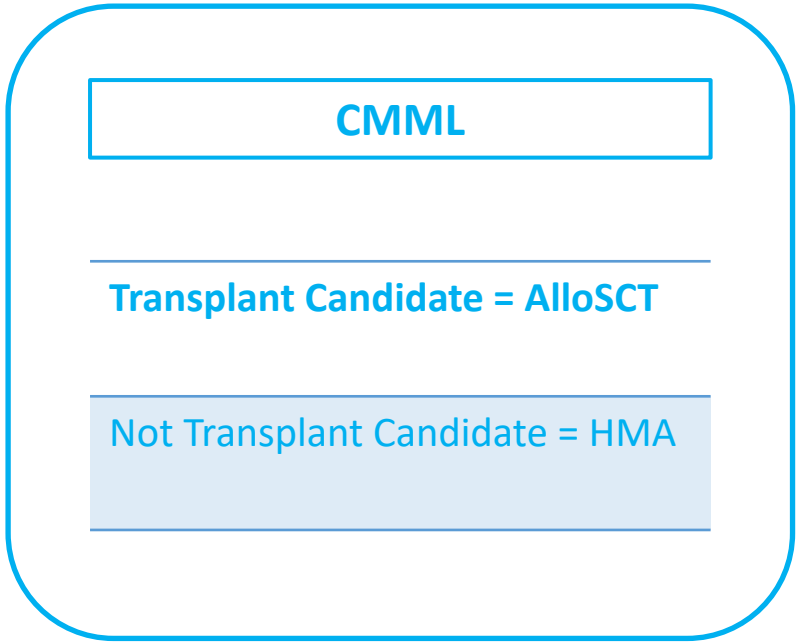
Monocytosis:	>1K
Associated Genes:	PDGFRA, PDGFRB, FGFR
Rule Out Related Conditions:	CML, secondary monocytosis

CMML Pathology

CMML is an overlap syndrome between MDS and MPN

CMML Types	Peripheral Blasts	BMB Blasts
Type 1	< 5%	< 10%
Type 2	5-20%	10-20%

CMML Treatment



MDS & MPN Review Handout

MDS Diagnosis

MDS

dysfunctional maturation of the bone marrow

UNDER-production of one or more cell line

MPN

dysfunctional activation of the bone marrow

OVER-production of one or more cell line

RISK FACTORS
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TYPES

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5q Disease

Lenalidomide

* Low/Intermediate IPSS

Low IPSS (non 5q)

EPO (if EPO < 500) +/- GCSF

Hypomethylating Agent (HMA)

ATG + Cyclosporine

Luspatercept (SF3B1+)

Lenalidomide

Clinical Trial

Intermediate/High IPSS (non 5q)

Transplant Candidate = HMA or ASCT

Not Transplant Candidate = HMA

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Three major mutations in MPN: JAK2, CALR, MPL

JAK2

- JAK/STAT proliferation pathway
- Most common mutation in MPN
- 90% PV
- 50-60% ET/PMF

CALR

- Ca binding protein
- Rare in PV
- 70% of ET/PMF [w/o ΔJAK2]

MPL

- Encodes thrombopoietin receptor (TPO-R)

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GENETIC MUTATION	**JAK2, CALR, MPL**
BONE MARROW BIOPSY	**BM Fibrosis** Megakaryocyte proliferation, atypia
Extramedullary Hematopoiesis (Liver and Spleen)	**HSM** Tear drops

MPN Treatment

MPN RISK FACTORS
- Age > 60
- Thromboembolism

PMF TREATMENT PARADIGM

Low Risk + Asymptomatic → Observe

Low Risk + Symptomatic → Treat

Intermediate/High Risk → HSCT

PV LOW/HIGH RISK TREATMENT

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PV HIGH RISK TREATMENT

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IFN alpha

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Not Transplant Candidate = HMA