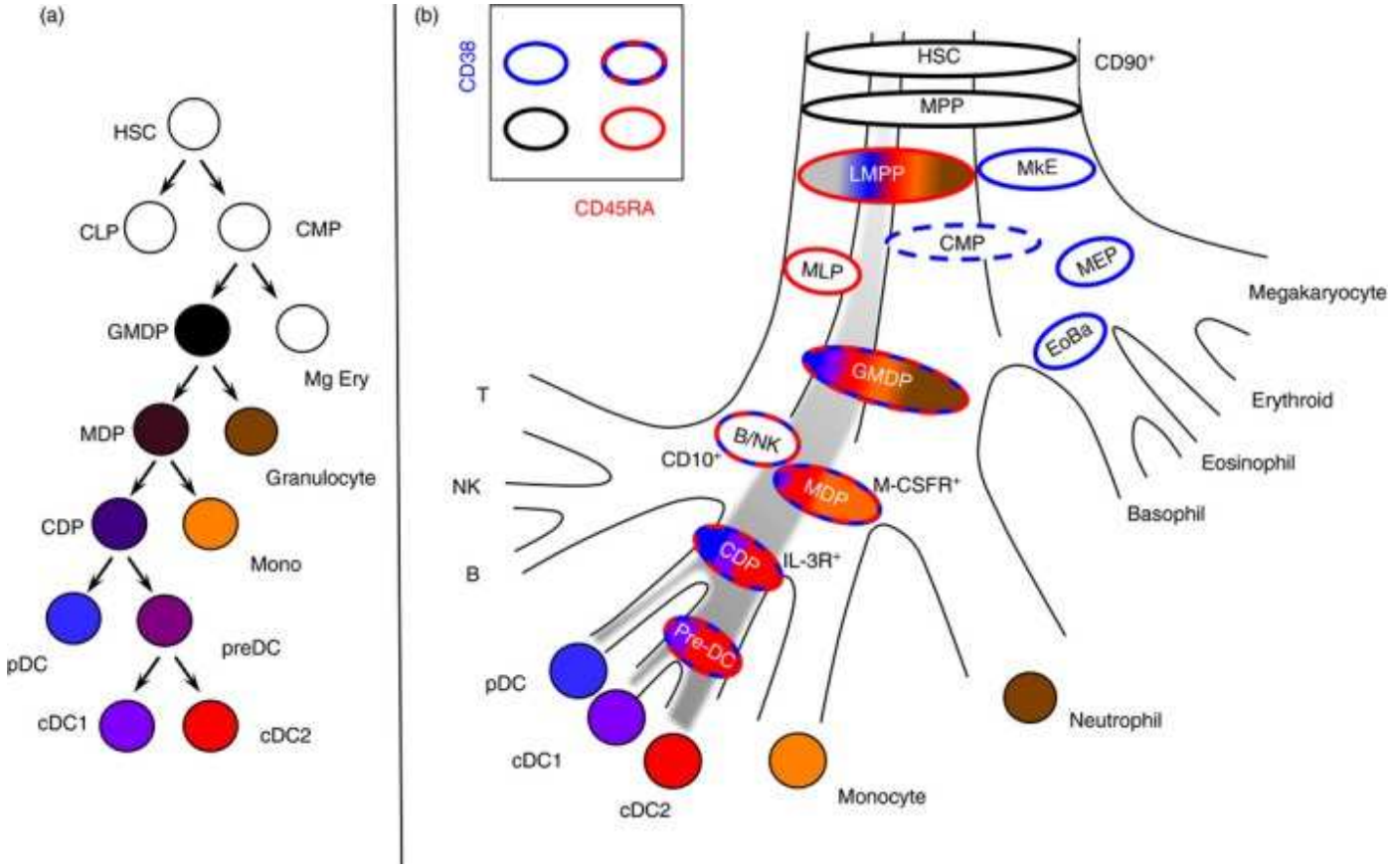
HEMATOLOGY

MYELOID SERIES DISORDERS

Kenneth Alonso, MD, FACP

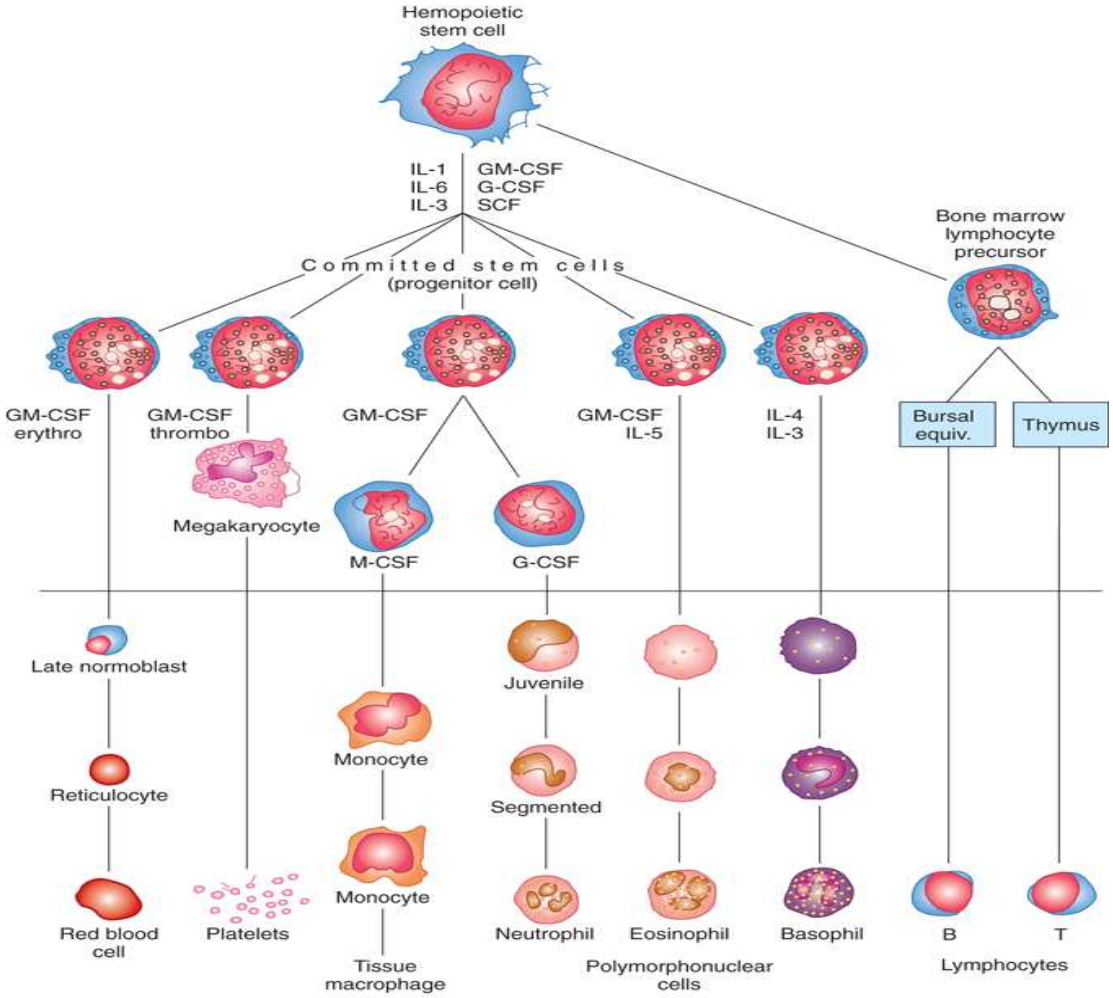
Classic and revised models of hematopoiesis



Common myeloid progenitors are mixtures of mega-erythroid and myeloid precursors and the most significant early partitioning of cell fate occurs when megakaryocyte and erythroid potentials separate from lympho-myeloid potentials.

Doi: 10.1111/imm.12888

Maturation of blood cells



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com
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Fig. 32-3
Accessed
02/01/2010

Myeloid series

- Myeloblasts are the least mature cells in the granulocyte lineage.
- Mononuclear, round-to-ovoid cells
- They may be distinguished from proerythroblasts by the finer, “grainy” reticular structure of their nuclei and the faintly basophilic cytoplasm.

Myeloid series

- Promyelocytes are the product of myeloblast division, and usually grow larger than their progenitor cells.
- During maturation, their nuclei show an increasingly coarse chromatin structure. T
- The nucleus is eccentric; the lighter zone over its bay-like indentation corresponds to the Golgi apparatus.
- The wide layer of basophilic cytoplasm contains copious large azurophilic granules containing peroxidases, hydrolases, and other enzymes.

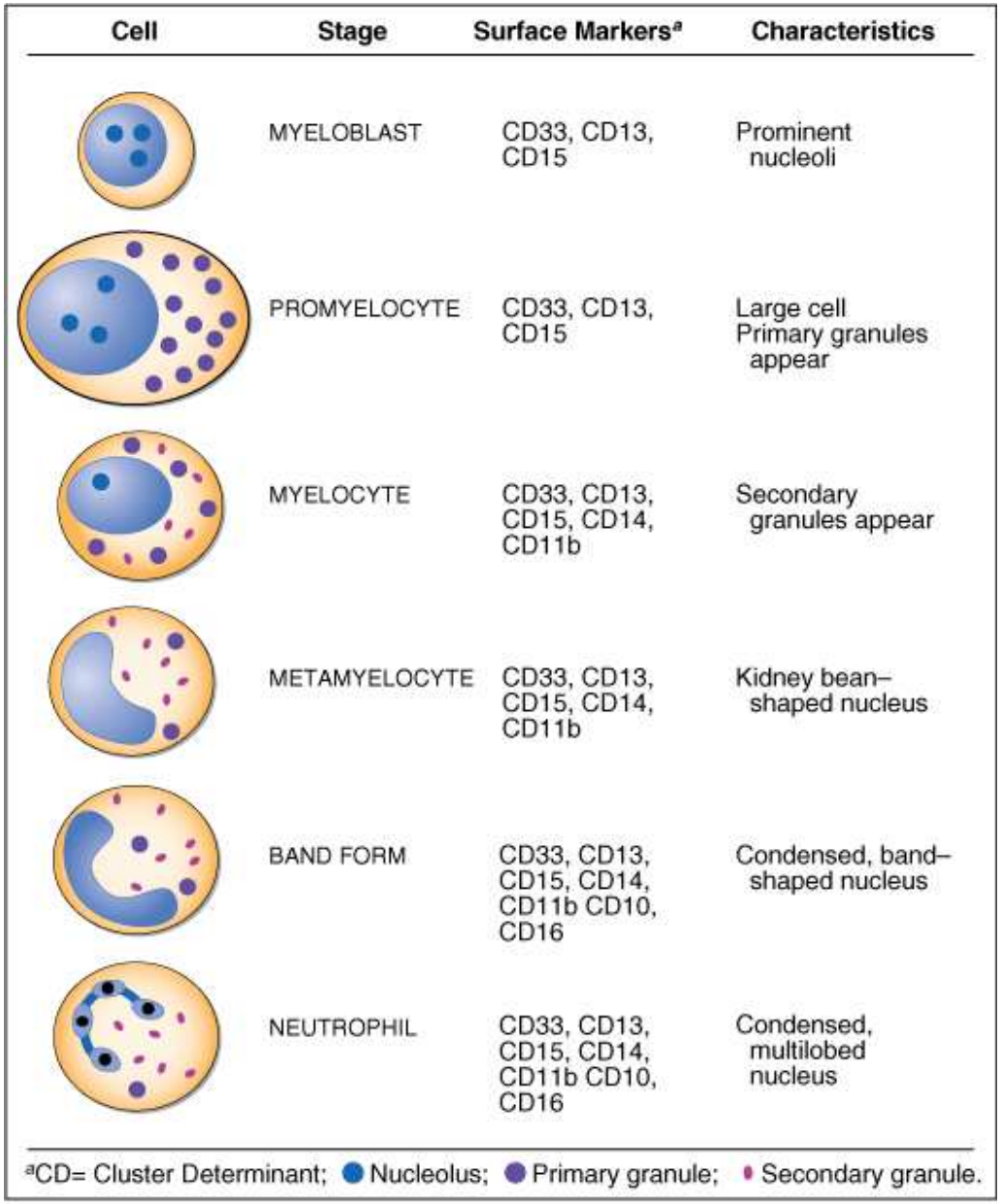
Myeloid series

- Myelocytes are the direct product of promyelocyte mitosis and are always clearly smaller than their progenitors.
- The ovoid nuclei have a banded structure
- The cytoplasm is becoming lighter with maturation and in some cases acquiring a pink tinge.
- A special type of granules, which no longer stain red like the granules in promyelocytes (“specific granules,” peroxidase-negative), are evenly distributed in the cytoplasm.

Myeloid series

- Metamyelocytes are the product of the final myelocyte division and show further maturation of the nucleus.
- The nuclei slowly take on a kidney bean shape and have some plasticity.
- Metamyelocytes are unable to divide.
- Further nuclear maturation occurs with nuclear contraction and segmentation.

Myeloid series maturation



Cell	Stage	Surface Markers[a]	Characteristics
	MYELOBLAST	CD33, CD13, CD15	Prominent nucleoli
	PROMYELOCYTE	CD33, CD13, CD15	Large cell Primary granules appear
	MYELOCYTE	CD33, CD13, CD15, CD14, CD11b	Secondary granules appear
	METAMYELOCYTE	CD33, CD13, CD15, CD14, CD11b	Kidney bean–shaped nucleus
	BAND FORM	CD33, CD13, CD15, CD14, CD11b CD10, CD16	Condensed, band–shaped nucleus
	NEUTROPHIL	CD33, CD13, CD15, CD14, CD11b CD10, CD16	Condensed, multilobed nucleus

[a]CD= Cluster Determinant; Nucleolus; Primary granule; Secondary granule.

Fig. 61-2
Accessed 03/01/2010

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

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Eosinophil series

- Eosinophils arise from the same stem cell population as neutrophils and mature in parallel with them. The earliest point at which eosinophils can be morphologically defined in the bone marrow is at the promyelocyte stage.
- Promyelocytes contain large granules that stain blue–red; not until they reach the metamyelocyte stage do these become a dense population of increasingly round, golden-red granules filling the cytoplasm.
- The nuclei of mature eosinophils usually have only two segments.

Basophil series

- Basophils mature in parallel with cells of the neutrophil lineage.
- The earliest stage at which they can be identified is the promyelocyte stage, at which large, black–violet stained granules are visible.
- In mature basophils, which are relatively small, these granules often overlie the two compact nuclear segments.
- Tissue basophils have a round nucleus underneath large basophilic granules. They are not found in blood.

Monocyte series

- Arises early in the myeloid series but does not demonstrate specific precursors that can be identified morphologically without special staining techniques.
- Most diversified of all cells.
- Their constant characteristic is an ovoid nucleus, usually irregular in outline, with invaginations and often pseudopodia-like cytoplasmic processes. The nuclear chromatin is fine. The basophilic cytoplasmic layer varies in width, stains a grayish color, and contains a scattered population of very fine reddish granules.

Megakaryocyte series

- Megakaryocytes reside in the bone marrow and have giant, extremely hyperploid nuclei (16 times the normal number of chromosome sets on average), which build up by endomitosis.
- Thrombopoietin regulates the increase of megakaryocytes and the release of thrombocytes.
- Cytoplasm with granules is pinched off from megakaryocytes to form thrombocytes.
- The residual naked megakaryocyte nuclei are phagocytosed.

Megakaryocyte series

- Only mature thrombocytes occur in blood.
- Very small and anuclear, their light blue stained cytoplasm and its processes give them a star-like appearance, with fine reddish blue granules near the center.
- Abnormalities present before anemia in megaloblastic disorders.

Clues from examination of the bone marrow

- Bone marrow cytology allows a quantitative assessment only in relative terms.
- In adults, normal marrow cellularity is 35–40%.
- The important ratio of red precursor cells to white cells is 1 : 2 for men and 1 : 3 for women.

Clues from examination of the bone marrow

- Shifts towards erythropoiesis are seen in all regenerative anemias.
- A left shift in the erythroid series is seen in regenerative anemias except hemolysis.
- A right shift in the erythroid series is seen in hemolytic conditions (nests of normoblasts).
- Atypical proerythroblasts predominate in megaloblastic anemia and erythremia.

Clues from examination of the bone marrow

- Shifts toward granulopoiesis are seen in all reactive processes and in all malignant processes of the white cell series.
- A left shift in the granulocyte series is observed in all reactive processes and at the start of neoplastic transformation. In acute leukemias, undifferentiated and partially matured blasts may predominate. In agranulocytosis, promyelocytes are most abundant.
- A right shift in the granulocyte series is diagnostically irrelevant.

Neutropenia

- Causes:
- (1) Inadequate or ineffective granulopoiesis
- Hypocellular marrow
- Suppression of hematopoietic stem cells
- Suppression of granulocyte precursors (usually drug related)
- Agranulocytosis may result from direct toxic damage to precursors (phenothiazines)
- Agranulocytosis may result from immune-mediated injury (sulfa drugs)
- Also noted in Large Granular Lymphocyte leukemia

Neutropenia

- Hypercellular marrow
- Megaloblastic anemia
- Myelodysplastic syndromes
- (2) Increased destruction or sequestration of neutrophils in the periphery.
- Hypercellular marrow
- Anti-neutrophil antibodies (e.g., SLE)
- Splenomegaly
- Serious infections are most likely when the absolute neutrophil count falls below 500/ul

Leukocytosis

- The peripheral blood leukocyte count is influenced by:
- The size of the precursor and storage cell pools in the bone marrow, thymus, circulation, and peripheral tissues
- The rate of release of cells from the storage pools into the circulation
- The proportion of cells that are adherent to blood vessel walls at any time (the marginal pool)
- The rate of extravasation of cells from the blood into tissues

Leukocytosis

- In acute infection there is a rapid increase in the egress of mature granulocytes from the bone marrow pool
- Mediated through the effects of TNF and IL-1.
- IL-5 mainly stimulates eosinophil production
- G-CSF induces neutrophilia.

Table 13-2 Mechanisms and Causes of Leukocytosis

Increased Production in the Marrow
Chronic infection or inflammation (growth factor-dependent)
Paraneoplastic (e.g., Hodgkin lymphoma; growth factor-dependent)
Myeloproliferative disorders (e.g., chronic myeloid leukemia; growth factor-independent)
Increased Release from Marrow Stores
Endotoxemia
Infection
Hypoxia
Decreased Margination
Exercise
Catecholamines
Decreased Extravasation into Tissues
Glucocorticoids

Morphologic change with infection

- Toxic granules are coarser and darker than the normal neutrophilic granules
- Represent abnormal azurophilic (primary) granules.
- Döhle bodies are patches of dilated endoplasmic reticulum that appear as sky-blue cytoplasmic “puddles.”
- Cytoplasmic vacuolization

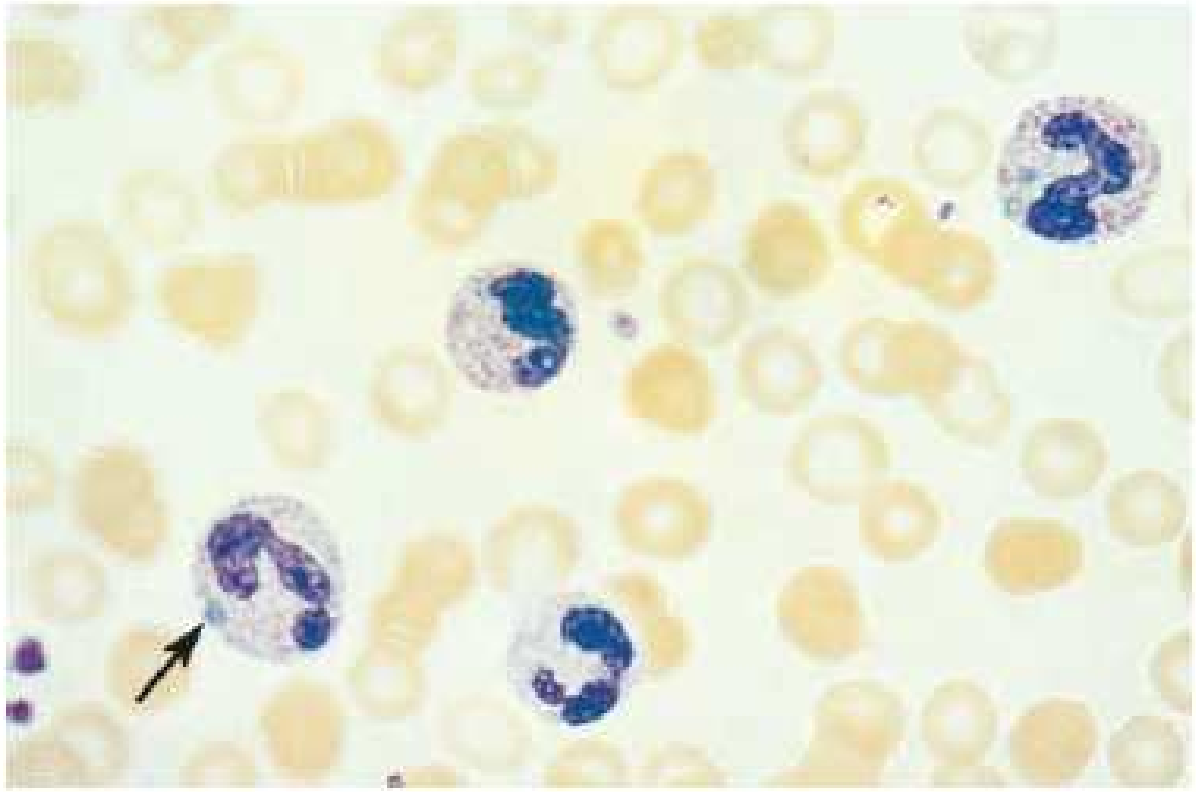


Figure 13-2 Reactive changes in neutrophils. Neutrophils containing coarse purple cytoplasmic granules (toxic granulations) and blue cytoplasmic patches of dilated endoplasmic reticulum (Döhle bodies, *arrow*) are observed in this peripheral blood smear prepared from a patient with bacterial sepsis.

Table 13-3 Causes of Leukocytosis

Type of Leukocytosis	Causes
Neutrophilic leukocytosis	Acute bacterial infections, especially those caused by pyogenic organisms; sterile inflammation caused by, for example, tissue necrosis (myocardial infarction, burns)
Eosinophilic leukocytosis (eosinophilia)	Allergic disorders such as asthma, hay fever, parasitic infestations; drug reactions; certain malignancies (e.g., Hodgkin and some non-Hodgkin lymphomas); autoimmune disorders (e.g., pemphigus, dermatitis herpetiformis) and some vasculitides; atheroembolic disease (transient)
Basophilic leukocytosis (basophilia)	Rare, often indicative of a myeloproliferative disease (e.g., chronic myelogenous leukemia)
Monocytosis	Chronic infections (e.g., tuberculosis), bacterial endocarditis, rickettsiosis, and malaria; autoimmune disorders (e.g., systemic lupus erythematosus); inflammatory bowel diseases (e.g., ulcerative colitis)
Lymphocytosis	Accompanies monocytosis in many disorders associated with chronic immunologic stimulation (e.g., tuberculosis, brucellosis); viral infections (e.g., hepatitis A, cytomegalovirus, Epstein-Barr virus); *Bordetella pertussis* infection

Myelodysplasia

- Myelodysplastic neoplasms present after a long course of bone marrow insufficiency with a deficit in all cell lines.
- Pass into a phase of insidiously increasing blast counts and from there into frank myelogenous leukemia
- 25-45% develop acute myelogenous leukemia (AML)
- >50 years of age
- Men have worse prognosis
- 50% asymptomatic
- Involves all tissues (including meninges and testes/ovaries).

Table 1. Myeloproliferative neoplasms.

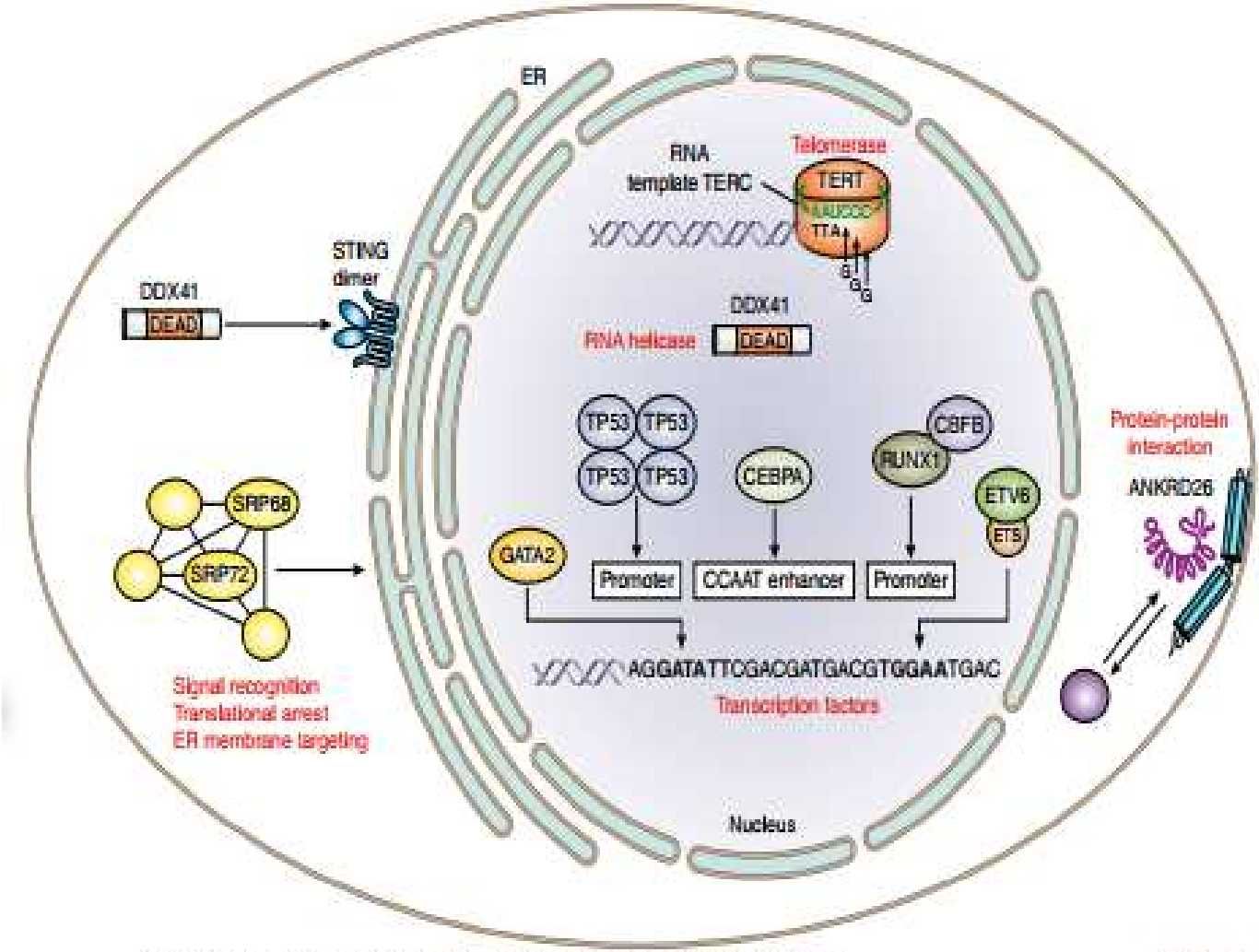
Chronic myeloid leukaemia
Polycythaemia vera
Essential thrombocythaemia
Primary myelofibrosis
Chronic neutrophilic leukaemia
Chronic eosinophilic leukaemia
Juvenile myelomonocytic leukaemia
Myeloproliferative neoplasm, not otherwise specified

Leukemia (2022) 36:1703 – 1719

Table 5. Myelodysplastic/myeloproliferative neoplasms.

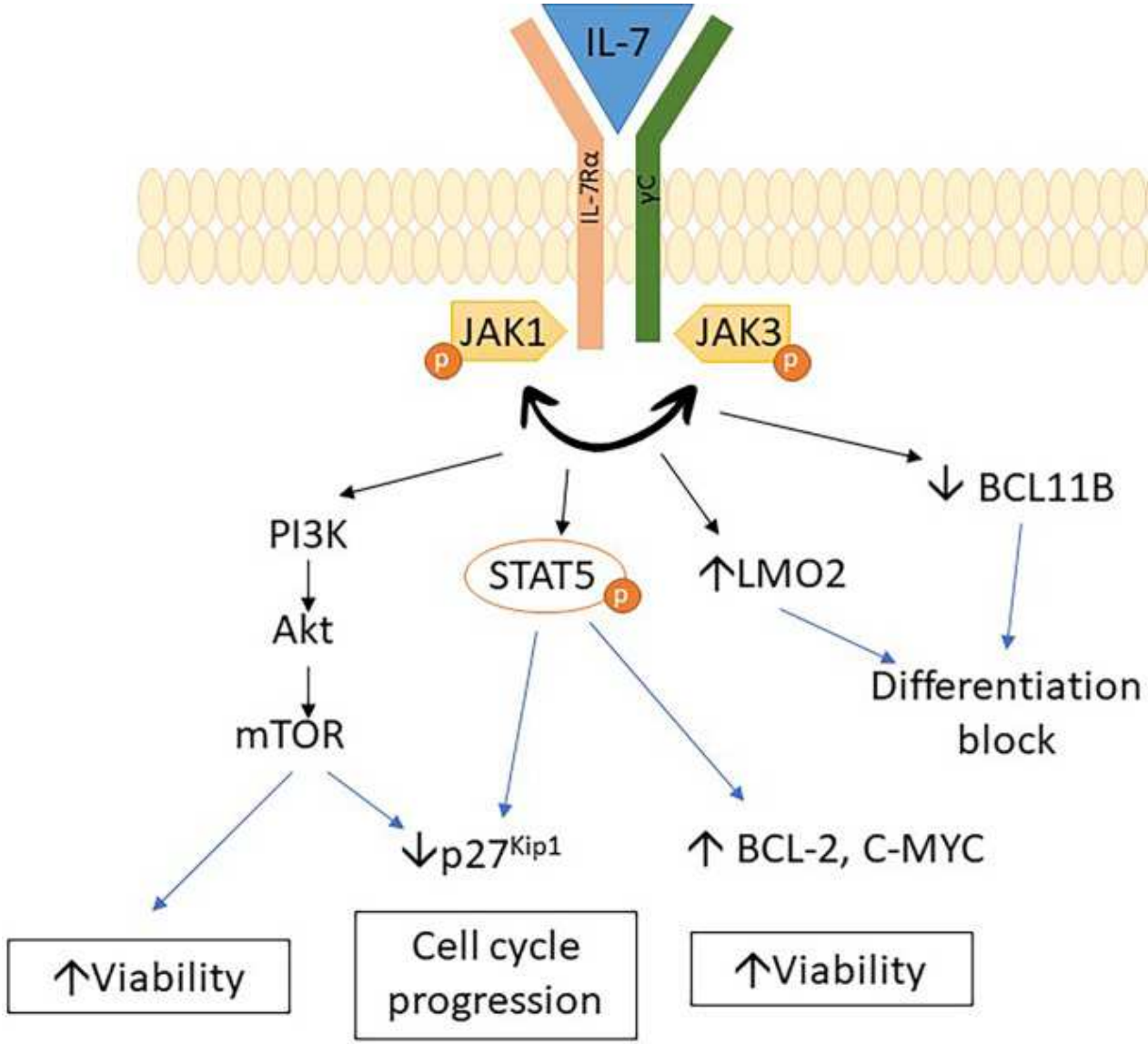
Chronic myelomonocytic leukaemia
Myelodysplastic/myeloproliferative neoplasm with neutrophilia
Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

Genetic predisposition to MDS



ER, Endoplasmic reticulum; MDS, myelodysplastic syndromes.

Fig. 5.1


IL-7
IL-7Rα
γC
JAK1
JAK3
P
P
PI3K
Akt
mTOR
STAT5
P
↑LMO2
↓ BCL11B
Differentiation block
↓p27Kip1
↑ BCL-2, C-MYC
↑Viability
Cell cycle progression
↑Viability

Myelodysplasia

- Acute leukemia may occur at any age.
- Fatigue and fever common.
- Hemorrhage occurs at a later stage.
- Transfusion dependence is associated with poor survival as iron overload leads to cardiac toxicity.
- Deferasirox (oral chelating agent) effective in treating iron overload.
- Untreated patients with iron overload survive 40 months
- With iron chelation, 160 months.

Myelodysplasia

- Macrocytic anemia
- Elevated levels of ferritin as well as B_{12}/Folic Acid
- Hb F elevated
- pseudo Pelger-Huet with low MPO, LAP, but increased muramidase and esterase
- Decreased platelet aggregation
- May have positive Ham's test
- Low cholinesterase
- Loss of A and H substance (increase Ii)

  Subset suppressed by CD8 and reversible with antithymocyte globulin

Myelodysplasia

- Some germline mutations (GATA2, RUNX1, TERT genes, etc.) predispose to MDS, and must be suspected in MDS diagnosed at <40 years, or if familial history of MDS or acute myeloid leukemia (AML).
- Macrocytic anemia is present in most MDS patients. Isolated neutropenia or thrombocytopenia are less frequent.
- In MDS patients, bone marrow is often hypercellular, but may also be normo- or hypocellular.

Myelodysplasia

- Dysplastic features can be seen in the blood but BM morphology is often more informative.
- The most frequent signs of dysgranulopoiesis include nuclear hypolobation (pseudo-Pelger-Huët) and hypogranularity.
- The presence of ringed sideroblasts is associated with somatic mutations in the spliceosome gene SF3B1.

Molecular alterations

- del 5, del 7 most common abnormalities
- del 5 and del 7 seen with alkylator use or mutagen exposure
- No correlation with classifications
- 5q23-31 contains GM-CSF, IL-3, 4, 5, PGDF, EGF, dihydrofolate reducatse, glucocorticoid receptor and flanked by M-CSF and C-fms (encode for M-CSF receptor)
- Frequent alterations associated with good prognosis include -Y, del(20q) and non-complex del(5q), in addition to normal karyotype.

Molecular alterations

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- No correlation with classifications
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Molecular alterations

- Frequent alterations associated with poor prognosis include del 7, trisomy 8, and complex karyotypes
- Monosomy 7 associated with poor chemotaxis (lack gp130)
- Mutations in genes involved in splicing (SF3B1, SRSF2, U2AF1, ZRSR2) are among the most frequent and are relatively specific to MDS and AML post-MDS.

Molecular alterations

- N-RAS abnormalities in 25%
- Predict early evolution to leukemia
- K-RAS abnormalities in 10% and disappear with remission following cytarabine
- H-RAS abnormalities in <10%
- Considered early preleukemic event
- erb-B found with t(1,7)
- C-fms in15%
- Ia (HLA-DR), CD33, CD34 high; low CD11b predict early leukemic conversion
- Marrow cultures may identify prednisone responsive clones

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Table 10. Subtypes of myeloid neoplasms associated with germline predisposition.

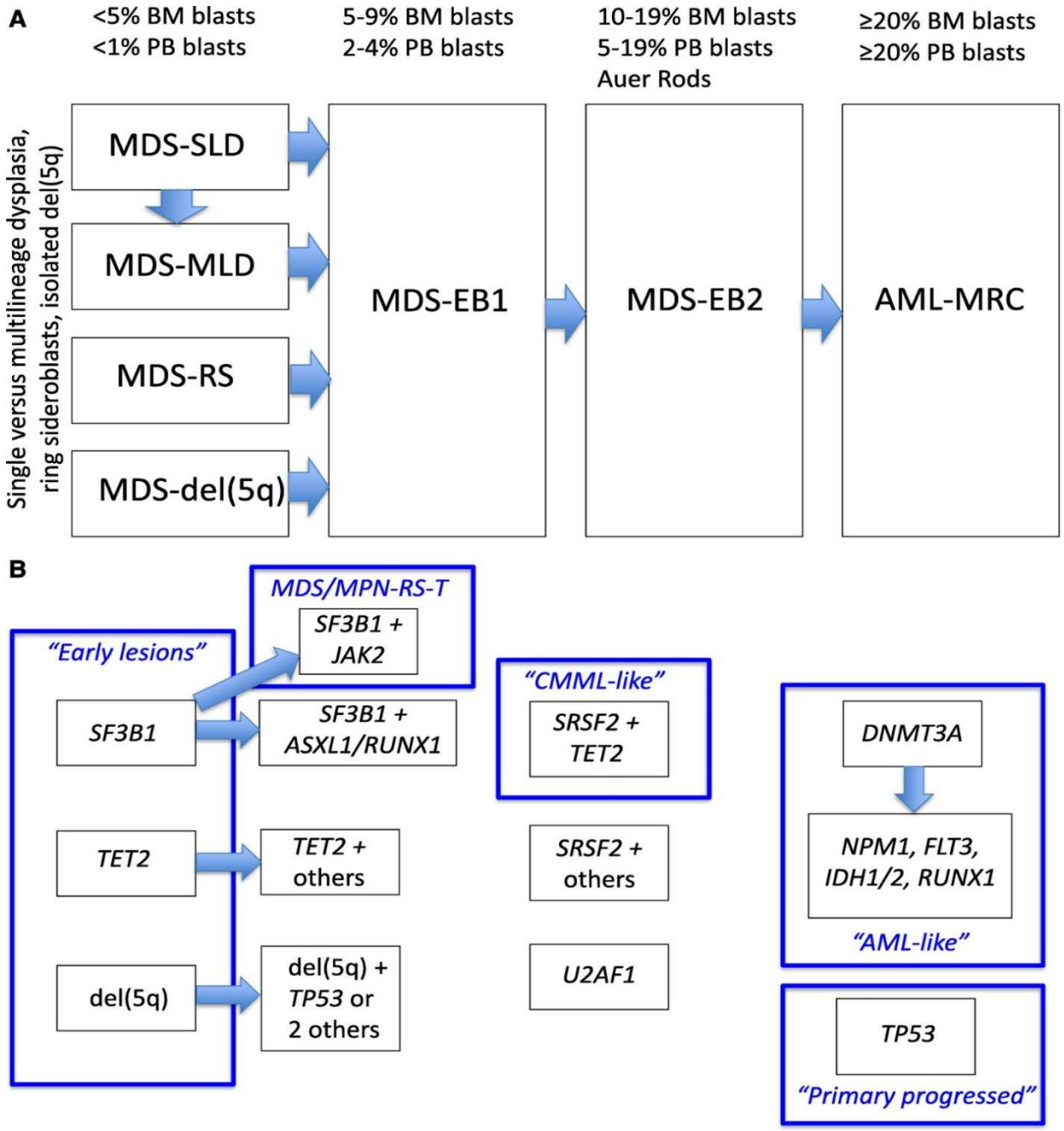
Myeloid neoplasms with germline predisposition without a pre-existing platelet disorder or organ dysfunction
• Germline *CEBPA* P/LP variant (CEBPA-associated familial AML)
• Germline *DDX41* P/LP variant[a]
• Germline *TP53* P/LP variant[a] (Li-Fraumeni syndrome)
Myeloid neoplasms with germline predisposition and pre-existing platelet disorder
• Germline *RUNX1* P/LP variant[a] (familial platelet disorder with associated myeloid malignancy, FPD-MM)
• Germline *ANKRD26* P/LP variant[a] (Thrombocytopenia 2)
• Germline *ETV6* P/LP variant[a] (Thrombocytopenia 5)
Myeloid neoplasms with germline predisposition and potential organ dysfunction
• Germline *GATA2* P/LP variant (GATA2-deficiency)
• Bone marrow failure syndromes
◦ Severe congenital neutropenia (SCN)
◦ Shwachman-Diamond syndrome (SDS)
◦ Fanconi anaemia (FA)
• Telomere biology disorders
• RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders[a,b])
• Down syndrome[a,b]
• Germline *SAMD9* P/LP variant (MIRAGE Syndrome)
• Germline *SAMD9L* P/LP variant (SAMD9L-related Ataxia Pancytopenia Syndrome)[c]
• Biallelic germline *BLM* P/LP variant (Bloom syndrome)

[a]Lymphoid neoplasms can also occur.
[b]See respective sections.
[c]Ataxia is not always present.
P pathogenic, *LP* likely pathogenic.

Table 4. Childhood myelodysplastic neoplasms (MDS).

	Blasts
Childhood MDS with low blasts	<5% BM; <2% PB
Hypocellular	
Not otherwise specified	
Childhood MDS with increased blasts	5–19% BM; 2–19% PB

BM bone marrow, *PB* peripheral blood.



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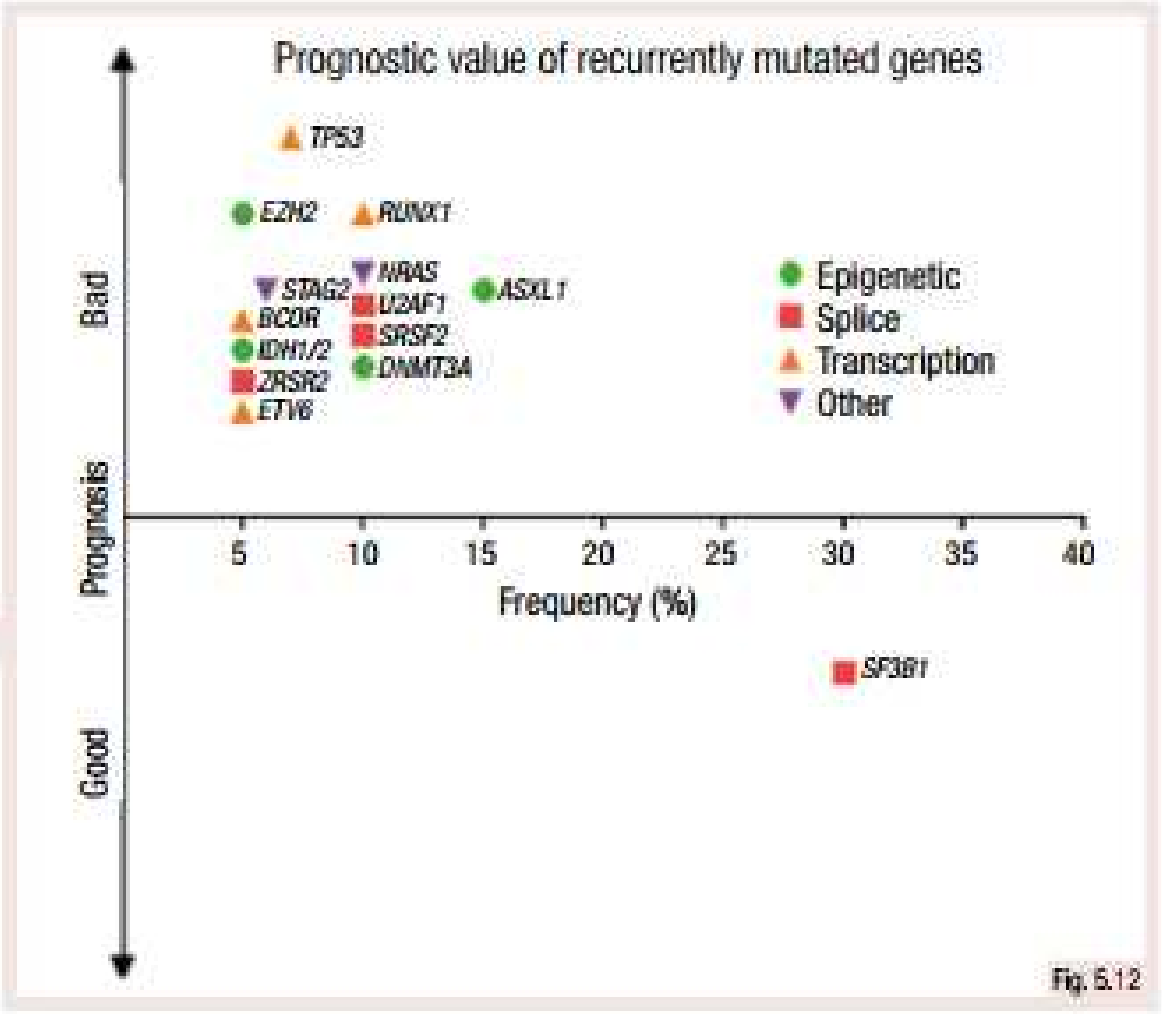

Prognostic value of recurrently mutated genes
TP53
EZH2
RUNX1
NRAS
STAG2
U2AF1
ASXL1
BCOR
SRSF2
IDH1/2
DNMT3A
ZRSR2
ETV6
Epigenetic
Splice
Transcription
Other
Bad
Prognosis
Good
5
10
15
20
25
30
35
40
Frequency (%)
SF3B1

Fig. 5.12

WHO classification

- MDS with ring sideroblasts (MDS-RS):
- 80%, mutations in the spliceosome gene SF3B1 at 2q33.1
- Binds pre-mRNA upstream of intron's branch site
- 5 year median survival
- Must not meet criteria for isolated del(5q)
- Blasts < 5% BM, < 1% PB, no Auer rods
- MDS-RS and single lineage dysplasia (former RARS):
- 1 dysplastic lineage, 1 - 2 cytopenias

WHO classification

- MDS-RS and multilineage dysplasia:
- 2 - 3 dysplastic lineages, 1 - 3 cytopenias
- MDS with single lineage dysplasia:
- 1 dysplastic lineage, 1 - 2 cytopenias
- Blasts < 5% BM, < 1% PB, no Auer rods
- Does not meet criteria for MDS-RS or MDS with isolated del(5q)

WHO classification

- MDS with isolated del(5q):
- The only cytogenetic abnormality that defines a subtype
- None or any ring sideroblasts
- 1 - 3 dysplastic lineages, 1 - 2 cytopenias
- Blasts < 5% BM, < 1% PB, no Auer rods
- 2:1 women
- >50 years old
- 25% splenomegaly
- Thrombocytosis

WHO classification

- Generally good prognosis (5 year median survival)
- if additional cytogenetic abnormality such as monosomy 7 or del(7q), 40% progress to Acute Myelogenous Leukemia with 4-11 month survival
- TP53 mutation is also associated with poor prognosis

WHO classification

- MDS with excess blasts:
- 1 - 3 dysplastic lineages, 1 - 3 cytopenias
- None or any ring sideroblasts
- MDS-EB-1:
- Blasts 5 - 9% BM or 2 - 4% PB, no Auer rods
- MDS-EB-2:
- Blasts 10 - 19% BM or 5 - 19% PB or Auer rods

WHO classification

- MDS, unclassifiable:
- MDS-U with 1% blood blasts:
- 1 - 3 dysplastic lineages, 1 - 3 cytopenias
- None or any ring sideroblasts
- < 5% BM blasts
- MDS-U with SLD and pancytopenia:
- 1 dysplastic lineage, pancytopenia
- None or any ring sideroblasts
- Blasts < 5% BM, < 1% PB, no Auer rods

WHO classification

- MDS-U based on defining cytogenetic abnormality:
- 0 dysplastic lineages, 1 - 3 cytopenias,
- < 15% ring sideroblasts
- Blasts < 5% BM, < 1% PB, no Auer rods
- MDS defining cytogenetic abnormality

WHO classification

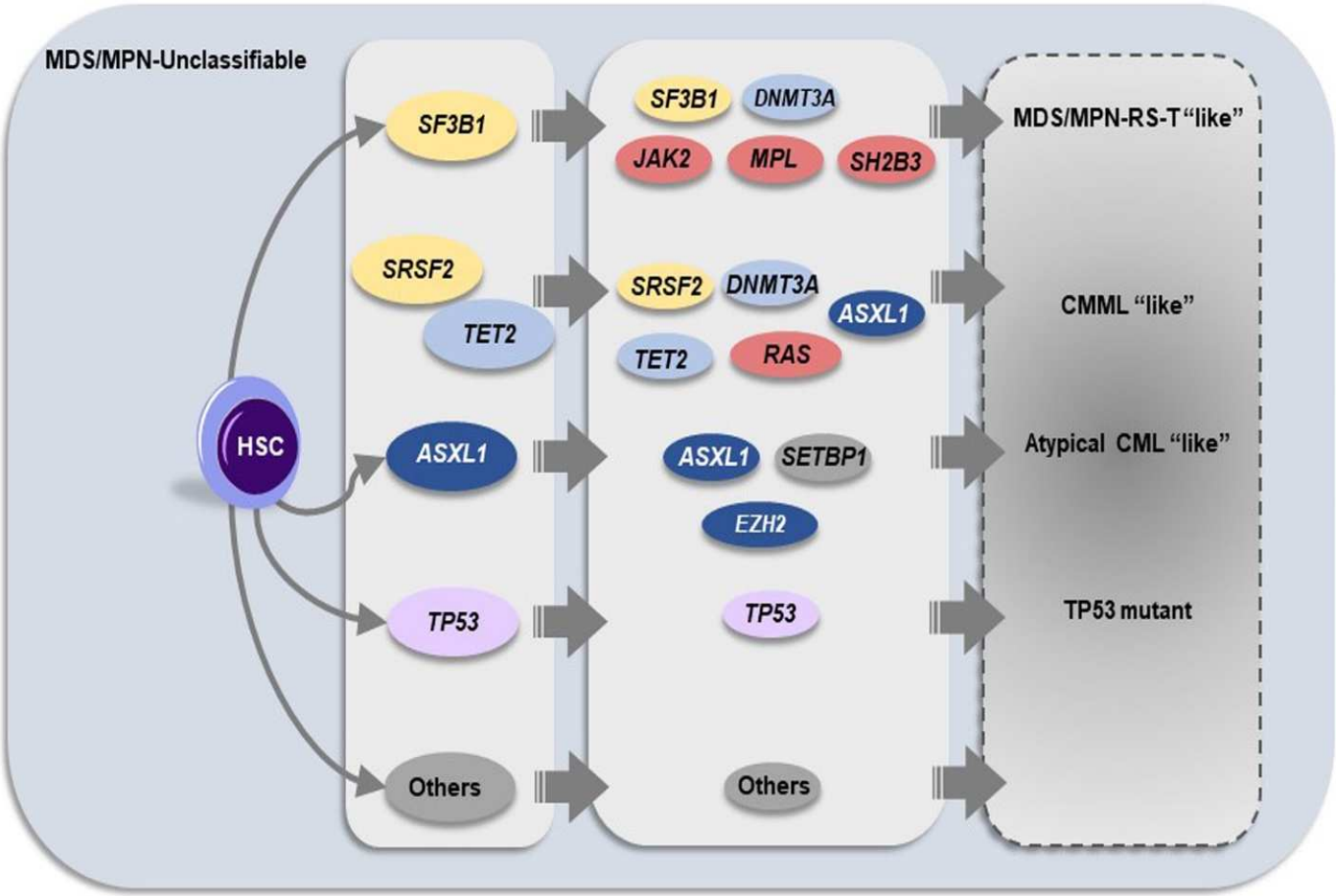
- Refractory anemia with excess blasts in transformation
- >5% blasts in peripheral blood; 20-30% blasts in marrow; Auer rods
- Includes marrows that appear leukemic but <30% blasts
- 1-1.5% annual incidence post chemotherapy
- May occur 4-7years post Hodgkin's disease or ovarian chemotherapy (but not at later times)
- May occur 2 years post topoisomerase inhibitor use (11q23 abnormality)

MDS defining cytogenetic abnormality

- Loss of chromosome 7 or del(7q)
- del(5q)
- Isochromosome 17q or t(17p)
- Loss of chromosome 13 or del(13q)
- del(11q)
- del(12p) or t(12p)
- del(9q)
- idic(X)(q13)

MDS defining cytogenetic abnormality

- t(11;16)(q23.3;p13.3)
- t(3;21)(q26.2;q22.1)
- t(1;3)(p36.3;q21.2)
- t(2;11)(p21;q23.3)
- inv(3)(q21.3;q26.2)/ t(3;3)(21.3;q26.2)
- t(6;9)(p23;q34.1)



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Cytogenetic Risk Group	IPSS-R Karyotype Abnormalities
Very good	del(11q), -Y
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, two or more independent clones
Poor	der(3q), -7, double with del(7q), complex with 3 abnormalities
Very Poor	Complex with > 3 abnormalities

IPSS-R Parameter	Categories and Associated Scores				
Cytogenetic Risk Group	Very good	Good	Intermediate	Poor	Very Poor
	0	1	2	3	4
Bone Marrow Blast %	≤ 2%	> 2% - < 5%	5% - 10%	> 10%	
	0	1	2	3	
Hemoglobin (g/dL)	≥ 10	8 - < 10	< 8		
	0	1	1.5		
Platelet Count (x 109/L)	≥ 100	50 - < 100	< 50		
	0	0.5	1		
Absolute Neutrophil Count (x 109/L)	≥ 0.8	< 0.8			
	0	0.5			

IPSS-R Risk Group	Points	% of Patients	Median survival, years	Time to 25% with AML, years
Very low	≤ 1.5	19%	8.8	Not reached
Low	> 1.5 - 3	38%	5.3	10.8
Intermediate	> 3 - 4.5	20%	3	3.2
High	> 4.5 - 6	13%	1.6	1.4
Very High	> 6	10%	0.8	0.73

https://ascopubs.org/doi/full/10.1200/EDBK_175397

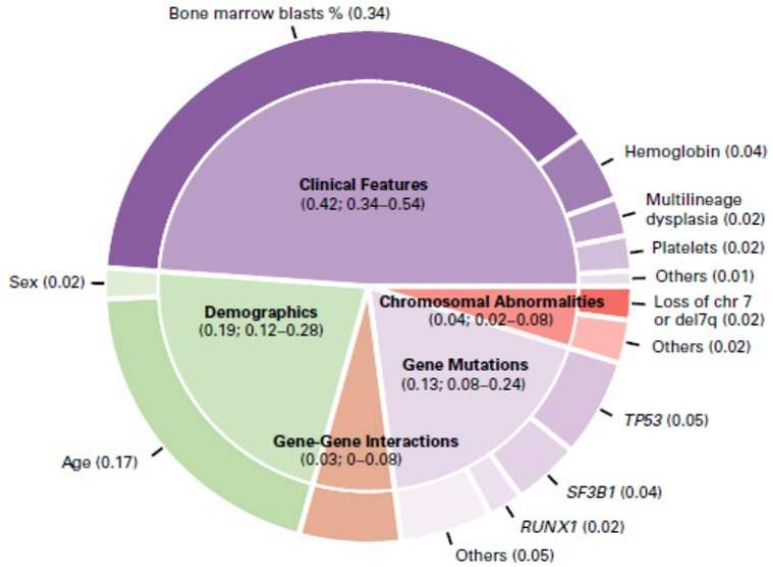
Myelodysplasia

- Favorable outcomes:
- Del 5q (15%), del 20q (5%), del 12p (1%), -Y (5%)
- Del 5q represents a functional loss of RPS14.
- The gene encodes a component of the 40S ribosomal subunit.
- Ribosomal assembly is compromised.
- Macrocytic anemia and thrombocytosis characterize the syndrome of del 5q MDS and is dependent upon p53 activation.
- Low levels of Foxp3+ T_{reg} allow the development of autoreactive T clones.
- Immunosuppressive.

Myelodysplasia

- Intermediate outcome
- Trisomy 8 (10%)
- Poor outcomes:
- 3q26 mutation (inv 3 or t(3;3) in 2%); or i17q or t17p mutation (2%); -7or del7q (10%); or FLT3/ITD, RUNX1, or p53 mutations; or myelofibrosis.

Blast percentage retains prognostic impact



Bersanelli M et al. JCO 2021;39:1223

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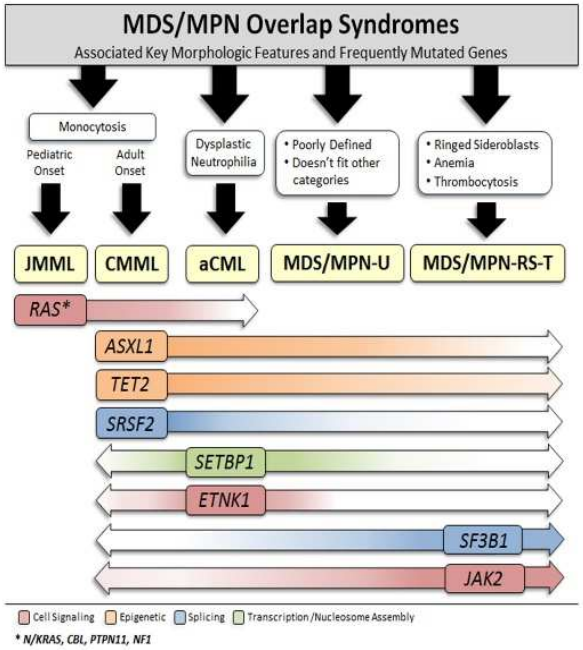

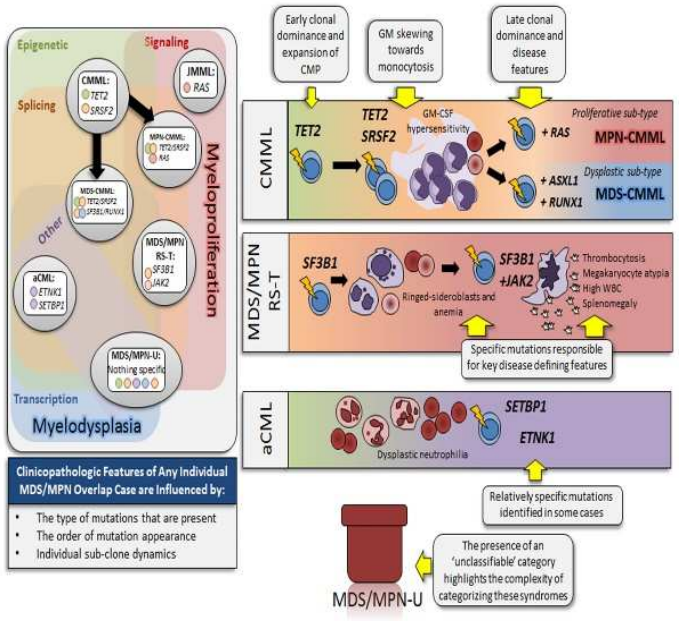

Patnaik M et al *Hematology Edu book* 2020

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Peripheral blood smear

- Erythroid:
- Dimorphic population of oval macrocytes and hypochromic microcytic red cells
- Basophilic stippling, erythrocyte vacuoles, nucleated red blood cells, Howell-Jolly bodies
- Granulocytes:
- Neutropenia with immature, hypogranular forms, pseudo-Pelger-Hüet neutrophils), monocytosis, myeloblasts
- Platelets:
- Thrombocytopenia, giant platelets

Bone marrow

- Erythroid:
- Erythroid hyperplasia, ringed sideroblasts
- Iron laden mitochondria visible as perinuclear granules with Prussian iron stain
- Megaloblastoid nuclear maturation
- Nuclear budding abnormalities
- Cytoplasmic vacuolization
- PAS positive erythroblasts

Bone marrow

- Leukocytes:
- Myeloblasts may be increased but < 20% of non-erythroid cells
- Or is defined as AML
- Abnormally localized immature precursors (ALIP)
- Aggregates (3 - 5) or clusters (6+) of immature precursors are remote from trabeculae (normal maturing granulocytes extend from trabeculae or blood vessels towards central areas)

Bone marrow

- Neutrophils with decreased secondary granules or pseudo Pelger-Hüet cells
- Toxic granulations, Döhle bodies, Auer rods
- Irregular nuclear segmentation
- increased basophils or monocytes
- Rarely monocytic nodules
- Myeloid cells are myeloperoxidase negative

Bone marrow

- Megakaryocytes:
- Megakaryocytes occur in clusters
- Single nuclear lobe, hypolobulation or multiple separate nuclei
- Micromegakaryocytes present

Spleen

- Splenomegaly uncommon
- Erythrophagocytosis, red pulp plasmacytosis, extramedullary hematopoiesis
- May see marked red pulp expansion due to monocytic proliferation
- Splenomegaly usually due to dyspoiesis, not proliferation

Refractory sideroblastic anemia

- MDS/MPN-RS-T is characterized by refractory anemia, medullar dyserythropoiesis with ring sideroblasts accounting for >15% of erythroid precursors, thrombocytosis with platelet count >450×10^9/L and <5% blasts on BM smear.
- Characterized by the combination of SF3B1 (70%–90% of cases) and JAK2/MPL/CALR (50%–70%) mutations.
- Prognosis is usually better than in other MDS/MPN.

Left panels: Abnormal megakaryocytes;
right panels: Ring sideroblasts (Perls' staining)

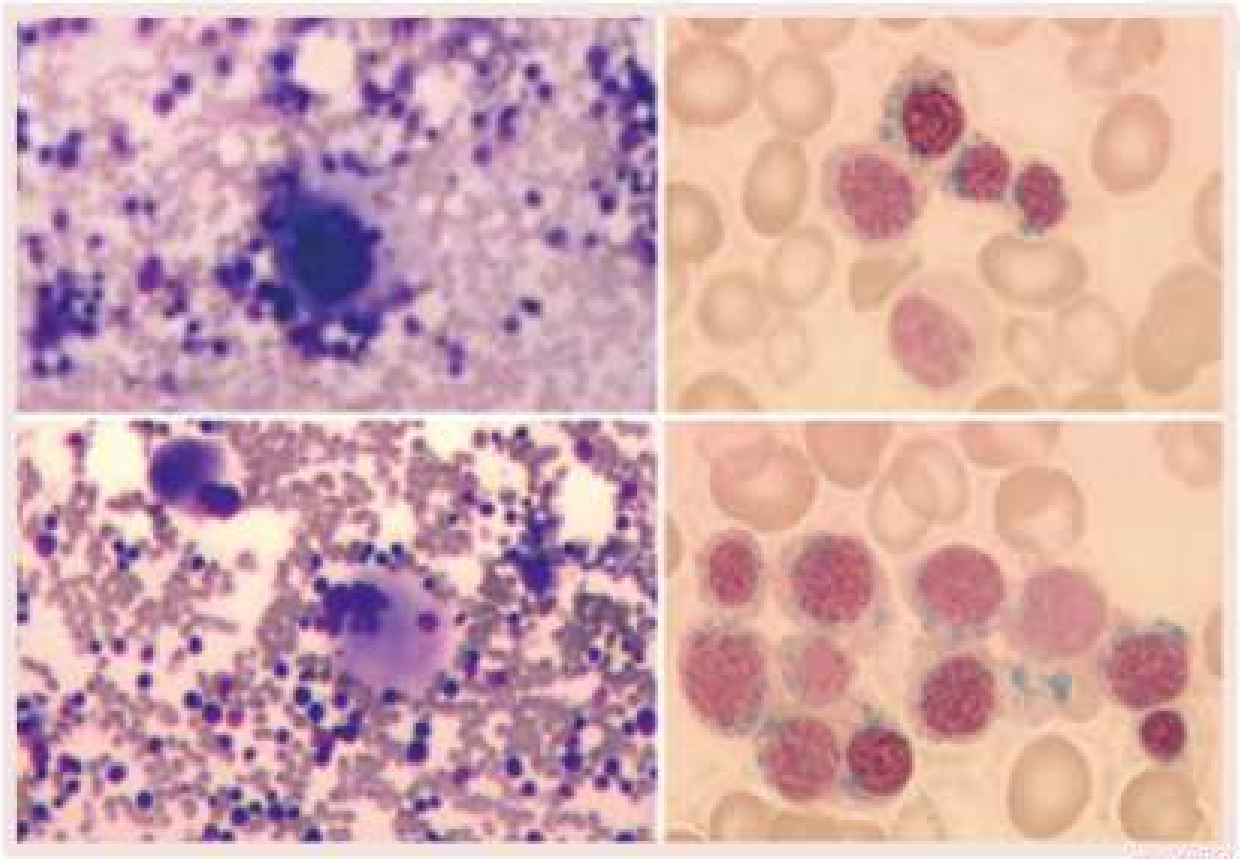
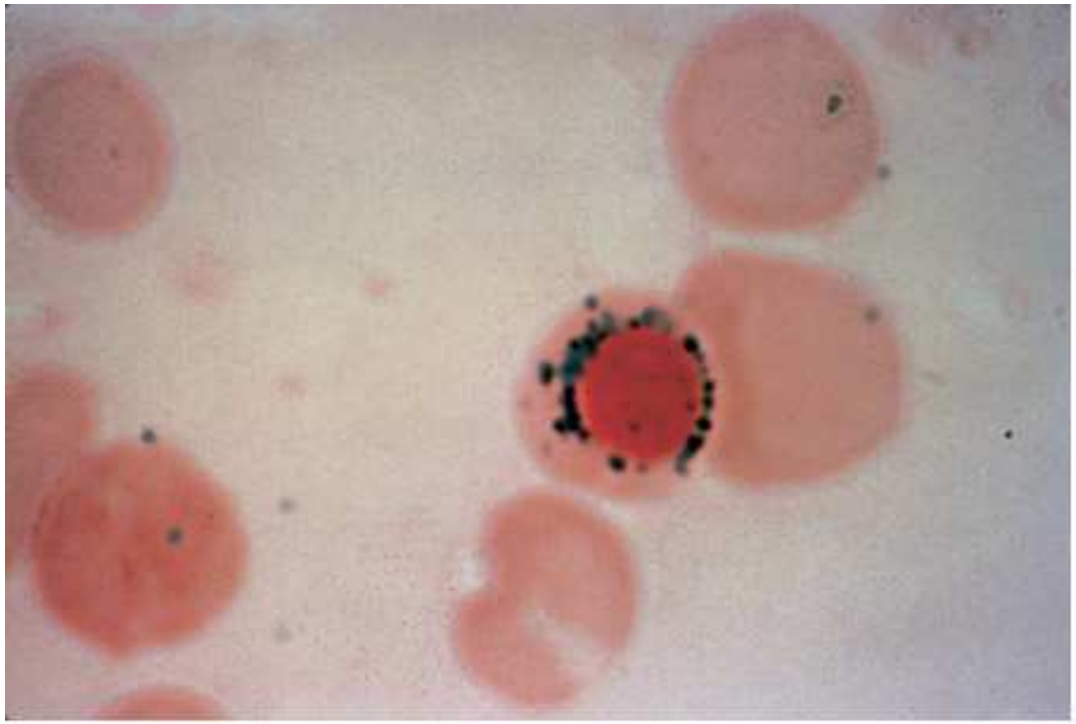


Fig. 15.8

Ringed sideroblast



An orthochromatic normoblast with a collar of blue granules (mitochondria encrusted with iron) surrounding the nucleus.

Fig. e11-39 Accessed 02/01/2010

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

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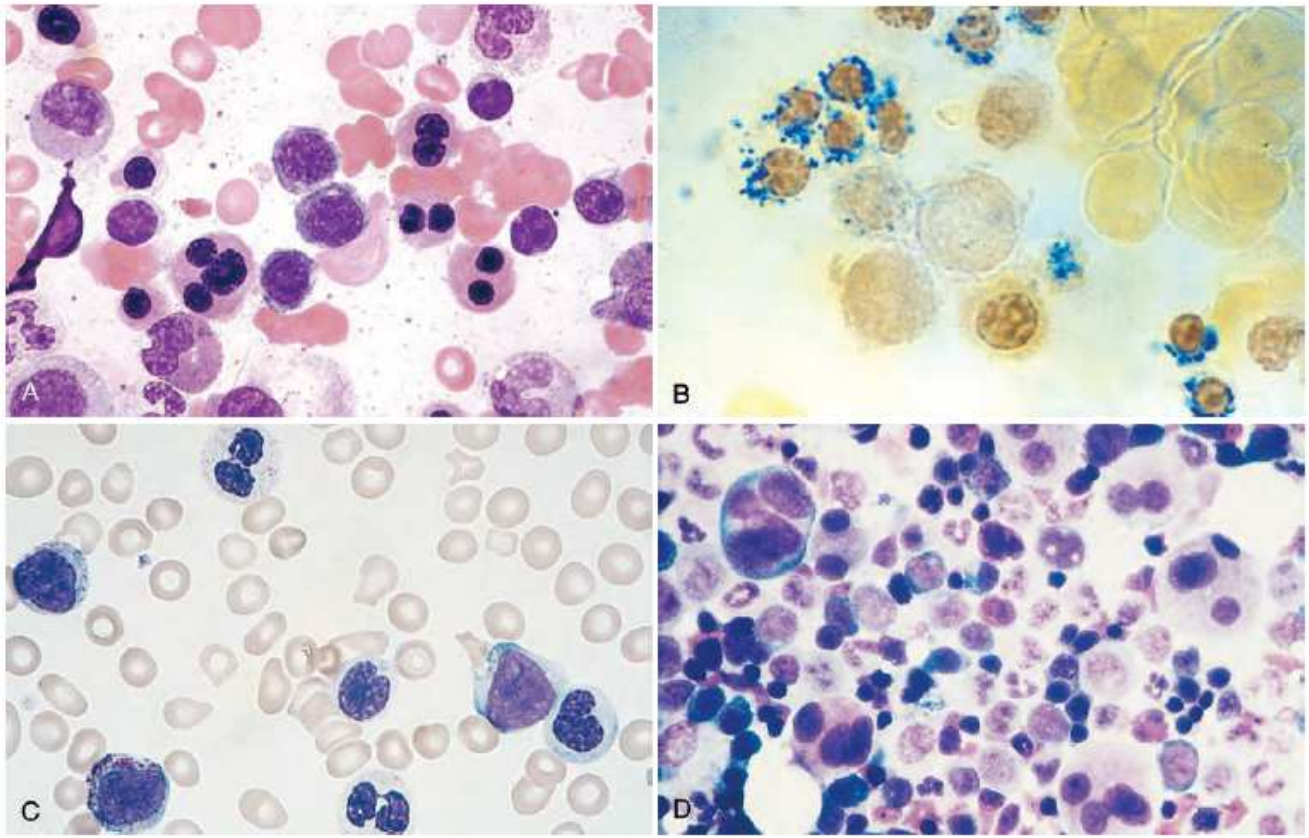


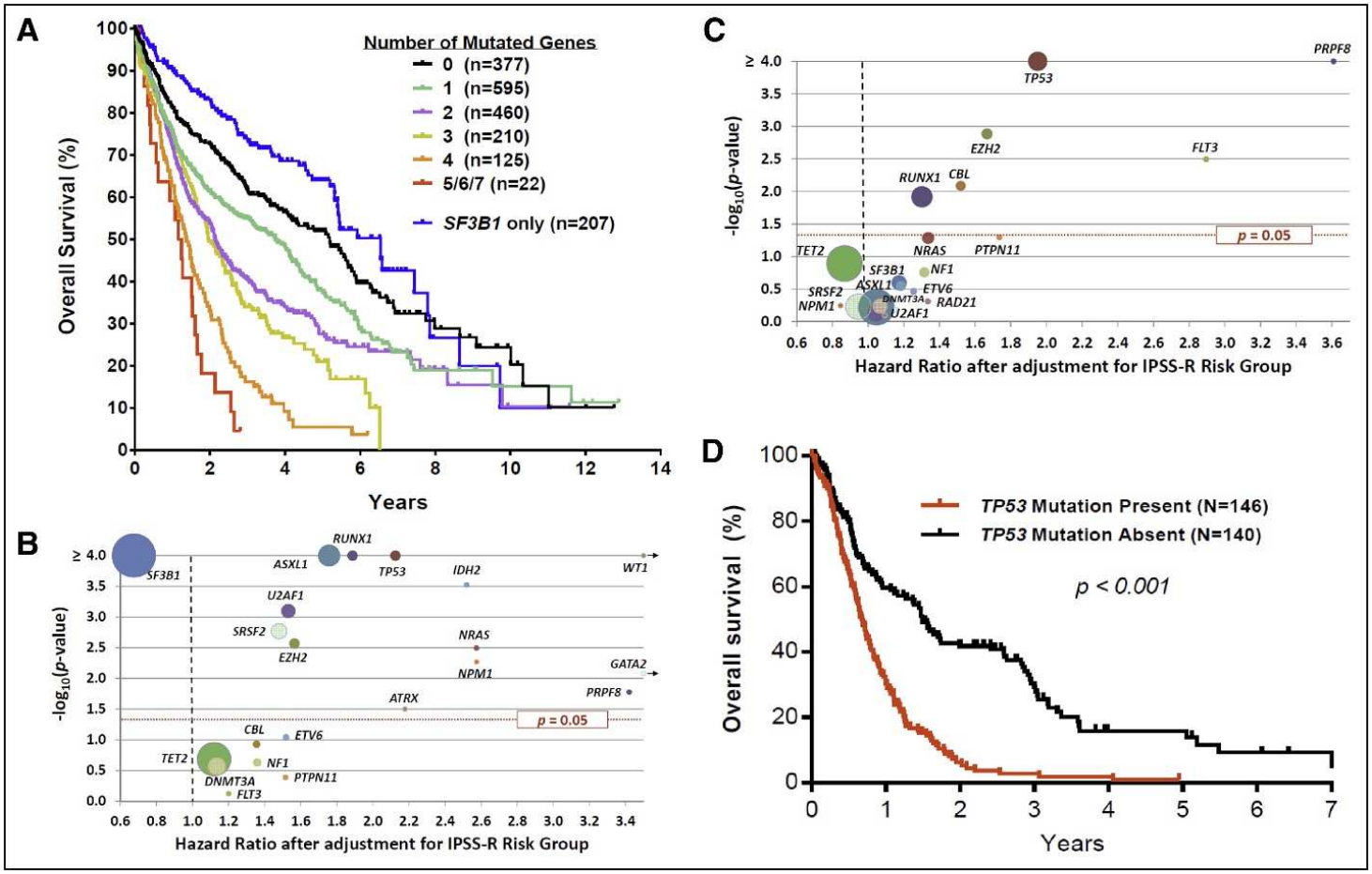
Figure 13-31 Myelodysplasia. Characteristic forms of dysplasia are shown. **A,** Nucleated red cell progenitors with multilobated or multiple nuclei. **B,** Ringed sideroblasts, erythroid progenitors with iron-laden mitochondria seen as blue perinuclear granules (Prussian blue stain). **C,** Pseudo-Pelger-Hüet cells, neutrophils with only two nuclear lobes instead of the normal three to four, are observed at the top and bottom of this field. **D,** Megakaryocytes with multiple nuclei instead of the normal single multilobated nucleus. (**A, B, D,** Marrow aspirates; **C,** peripheral blood smear.)

Prognosis

- TP53 mutation confers a markedly inferior prognosis to MDS, particularly when it is multihit
- Outcome uniformly poor irrespective of the blast percentage.
- MDS cases with t(3;3) or an inv(3) cytogenetic abnormality, even if classified as AML
- Outcome uniformly poor irrespective of the blast percentage.

Prognosis

- Blasts whose counts in the MDS range may bear mutations typically seen in de novo AML:
- NPM1, FLT3, IDH1, RUNX1.
- Splicing factor SF3B1 is closely associated with the presence of bone marrow ring sideroblasts in MDS
- Only mutation associated with relatively favorable prognosis



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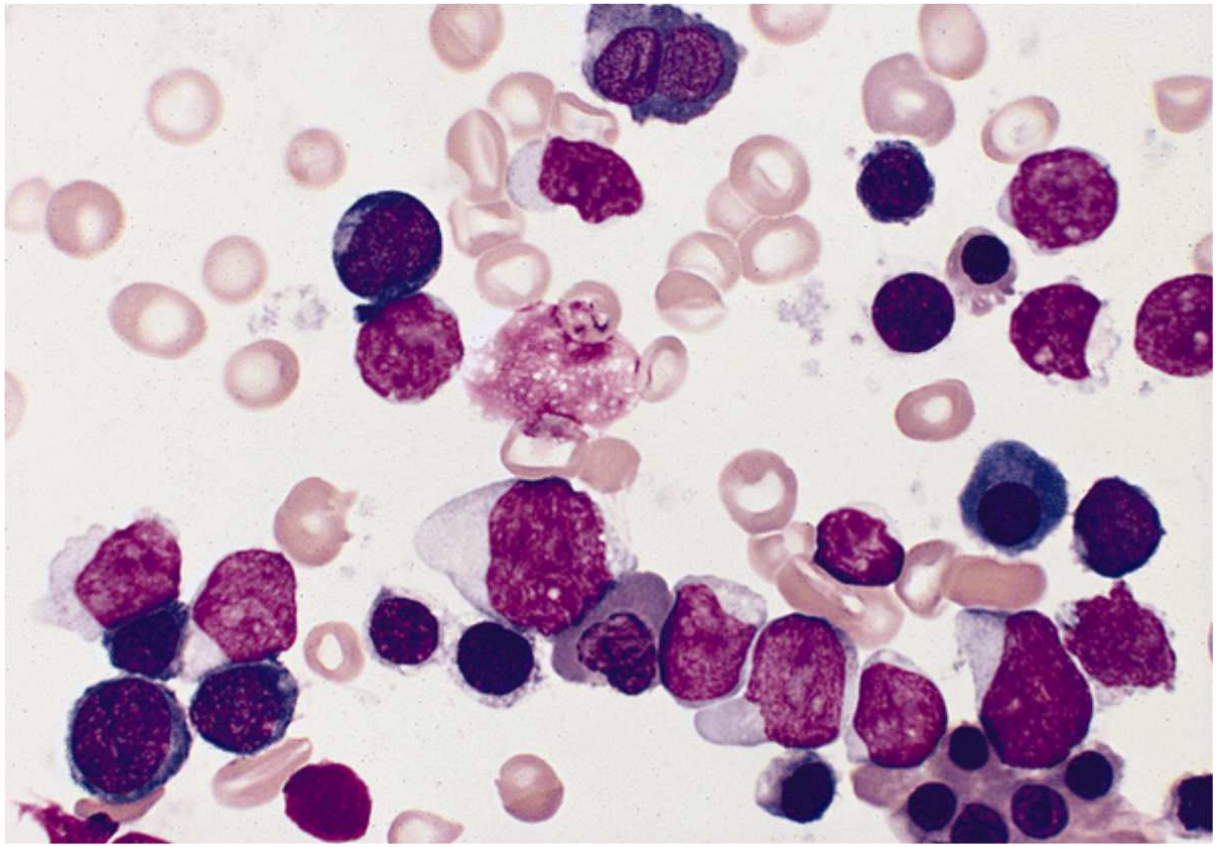
Erythroleukemia



Bone marrow smear from a patient with AML-M6 showing numerous myeloblasts and erythroid precursors at all stages of maturation. (Wright-Giemsa stain).

Fig. 81A

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Leukemia

- Acute leukemia represents a very aggressive, malignant transformation of an early hematologic precursor arrested in an immature, blast form.
- No longer has the ability to undergo maturation but may proliferate.
- Chronic leukemia is characterized by resistance to apoptosis and by accumulation of nonfunctional cells.
- Accumulation of cells in the marrow results in progressive hematopoietic failure, with associated infection, anemia, and thrombocytopenia.

Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Table 9. Differentiation markers and criteria for acute myeloid leukaemia (AML) types defined by differentiation.

Type	Diagnostic criteria*
AML with minimal differentiation	• Blasts are negative (<3%) for MPO and SBB by cytochemistry
	• Expression of two or more myeloid-associated antigens, such as CD13, CD33, and CD117
AML without maturation	• ≥3% blasts positive for MPO (by immunophenotyping or cytochemistry) or SBB and negative for NSE by cytochemistry
	• Maturing cells of the granulocytic lineage constitute <10% of the nucleated bone marrow cells
	• Expression of two or more myeloid-associated antigens, such as MPO, CD13, CD33, and CD117
AML with maturation	• ≥3% blasts positive for MPO (by immunophenotyping or cytochemistry) or SBB by cytochemistry
	• Maturing cells of the granulocytic lineage constitute ≥10% of the nucleated bone marrow cells
	• Monocyte lineage cells constitute < 20% of bone marrow cells
	• Expression of two or more myeloid-associated antigens, such as MPO, CD13, CD33, and CD117
Acute basophilic leukemia	• Blasts & immature/mature basophils with metachromasia on toluidine blue staining
	• Blasts are negative for cytochemical MPO, SBB, and NSE
	• No expression of strong CD117 equivalent (to exclude mast cell leukemia)
Acute myelomonocytic leukaemia	• ≥20% monocytes and their precursors
	• ≥20% maturing granulocytic cells
	• ≥3% of blasts positive for MPO (by immunophenotyping or cytochemistry)
Acute monocytic leukaemia	• ≥80% monocytes and/or their precursors (monoblasts and/or promonocytes)
	• <20% maturing granulocytic cells
	• Blasts and promonocytes expressing at least two monocytic markers including CD11c, CD14, CD36 and CD64, or NSE positivity on cytochemistry
Acute erythroid leukaemia	• ≥30% immature erythroid cells (proerythroblasts)
	• Bone marrow with erythroid predominance, usually ≥80% of cellularity
Acute megakaryoblastic leukaemia	• Blasts express at least one or more of the platelet glycoproteins: CD41 (glycoprotein IIb), CD61 (glycoprotein IIIa), or CD42b (glycoprotein Ib)[b]

*Shared diagnostic criteria include:

- ≥20% blasts in bone marrow and/or blood (except for acute erythroid leukaemia).
- Criteria for AML types with defined genetic alterations are not met.
- Criteria for mixed-phenotype acute leukaemia are not met (relevant for AML with minimal differentiation).
- Not fulfilling diagnostic criteria for myeloid neoplasm post cytotoxic therapy.
- No prior history of myeloproliferative neoplasm.

BM bone marrow, *MPO* myeloperoxidase, *NSE* nonspecific esterase, *PB* peripheral blood, *SBB* Sudan Black B.

Leukaemia	Main recurrent genetic aberrations in leukaemia in adults (frequency at diagnosis ≥5%)	
	Chromosomal aberrations	Gene mutations
ALL	Hyperdiploidy Hypodiploidy *t(9;22)/BCR-ABL1* *t(4;11)/MLL-AF4* Deletions of 9p incl. *CDKN2A/B* (9p21.3) *t(1;19)/TCF3-PBX* *t(12;22)/EP300-ZNF384*	*FAT1, SF1, CRLF2, TET2, PTPN11, CREBBP, MLL2, PAX5, SETD2, FLT3, RUNX1, DIS3, MPL, NRAS, KRAS, JAK2* *IKZF1* deletions and mutations *NOTCH1, FBXW7, JAK3, DNM2* (specifically in T-ALL)
AML	*t(8;21)/RUNX1-RUNX1T1* *inv(16)* or *t(16;16)/CBFB-MYH11* *t(15;17)/PML-RARA* Deletions of: 7q, 5q	*NPM1, DNMT3A, CEBPA, TET2, IDH1, IDH2, FLT3-ITD* (internal tandem duplication), FLT3-TKD (tyrosine kinase domain), *MLL*-PTD (partial tandem duplication), *ASXL1, NRAS, KRAS, TP53, WT1, PTPN11, RUNX1*
CLL	Deletions of: 13q14, 11q23, 17p Trisomy of chromosome 12 Rearrangements involving: 3p21, 11q23, 13q14, 14q32 and 18q21	*NOTCH1, ATM, PAX5, SF3B1, BIRC3, CHD2, TP53*
CML	*t(9;22)/BCR-ABL1*	*ABL1*-TKD (tyrosine kinase domain) Cause resistance to TKI; Not extensively studied for other mutations at diagnosis

Fig. 11.4

ALL, Acute lymphoblastic leukaemia; AML, acute myeloid leukaemia;
CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia;
T-ALL, T cell acute lymphoblastic leukaemia; TKI, tyrosine kinase inhibitor.

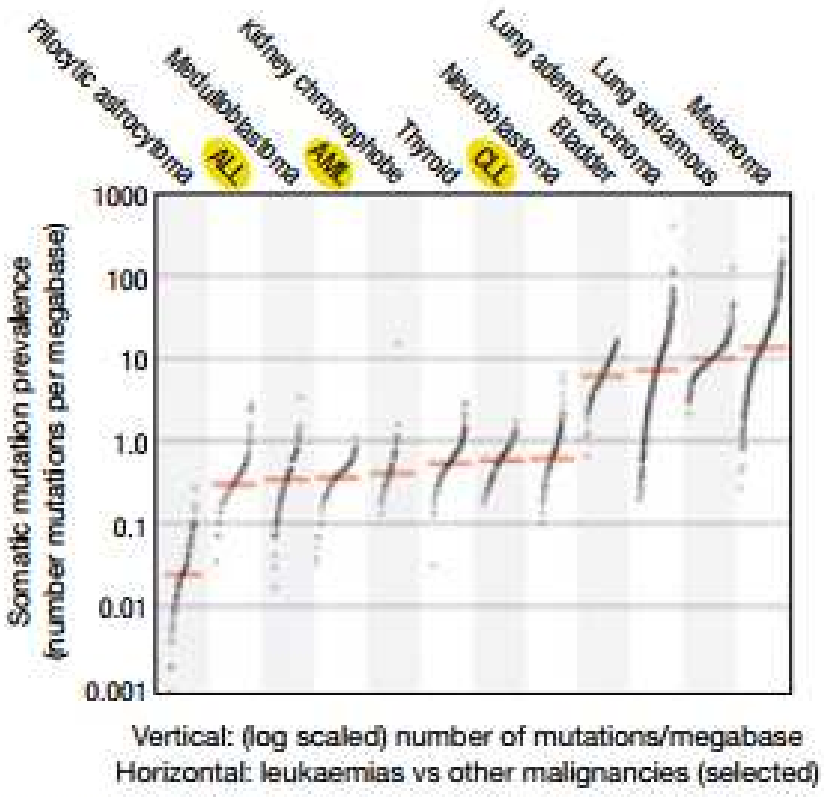


Fig. 11.6

ALL, Acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

2017 ELN risk stratification by genetics

Risk category	Genetic abnormality
Favourable	*t(8;21)(q22;q22.1); RUNX1-RUNX1T1* *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22); CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITDlow*
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITDhigh*
	Wild-type NPM1 without *FLT3*-ITD or with *FLT3*-ITDlow* (without adverse-risk genetic lesion)
	t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favourable or adverse
Adverse	*t(6;9)(p23;q34.1); DEK-NUP214*
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or *t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)*
	−5 or *del(5q); −7; −17/abn(17p)*
	Complex karyotype**, monosomal karyotype***
	Wild-type *NPM1* and *FLT3*-ITDhigh
	Mutated *RUNX1*
	Mutated *ASXL1*
	Mutated *TP53*

Fig. 1.10

*Low, low allelic ratio (<0.5), high, high allelic ratio (≥0.5)
**Three or more unrelated chromosome abnormalities in the absence of WHO-designated recurring translocations
***Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality
ELN, European LeukemiaNet; ITD, internal tandem duplication; WHO, World Health Organization.

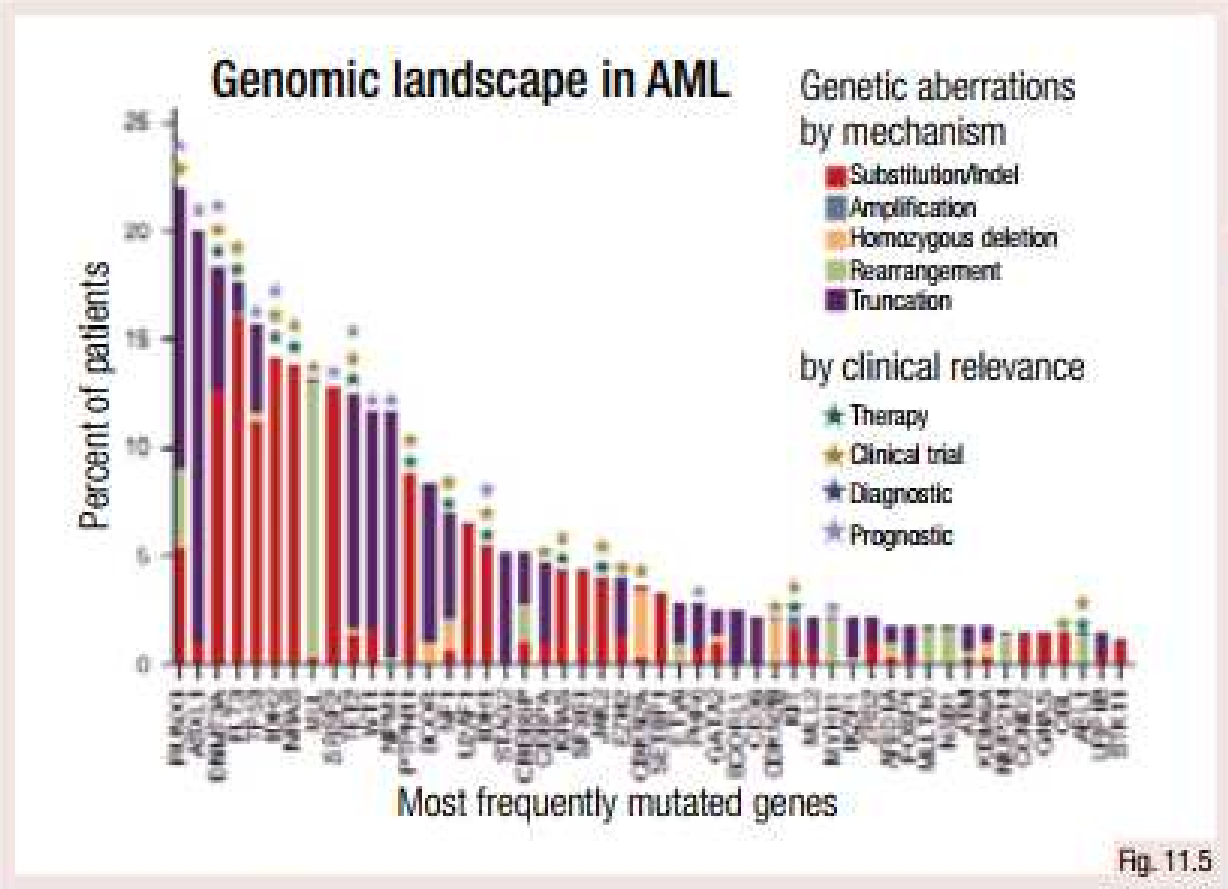
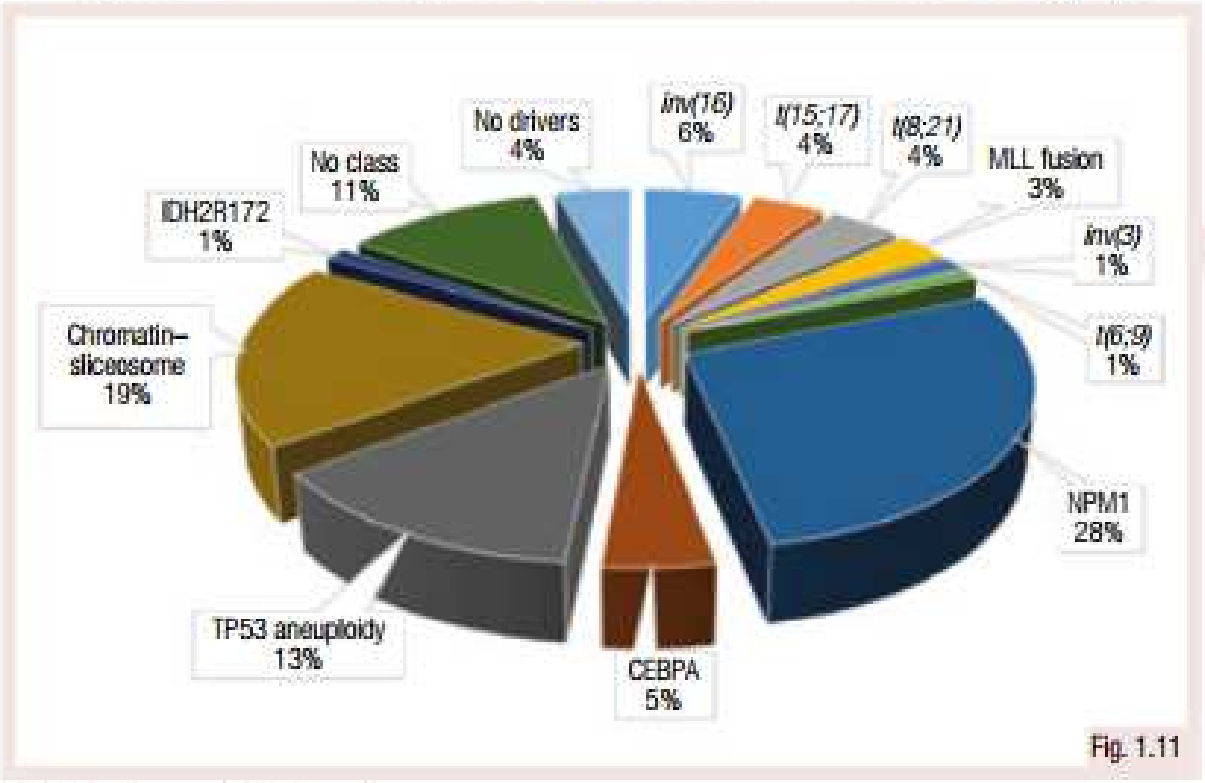


Fig. 11.5

AML, Acute myeloid leukaemia.

Proposed new AML classification scheme discriminates 13 subgroups



AML, Acute myeloid leukaemia.

Specific chromosomal aberrations such as t(8;21), inv(16), t(15;17) are disease-defining, irrespective of the quantified blast count.

Table 13-10 Major Subtypes of AML in the WHO Classification

Class	Prognosis	Morphology/Comments
I. AML with Genetic Aberrations		
AML with t(8;21)(q22;q22); *RUNX1/ETO* fusion gene	Favorable	Full range of myelocytic maturation; Auer rods easily found; abnormal cytoplasmic granules
AML with inv(16)(p13;q22); *CBFB/MYH11* fusion gene	Favorable	Myelocytic and monocytic differentiation; abnormal eosinophilic precursors with abnormal basophilic granules
AML with t(15;17)(q22;11-12); *RARA/PML* fusion gene	Intermediate	Numerous Auer rods, often in bundles within individual progranulocytes; primary granules usually very prominent, but inconspicuous in microgranular variant; high incidence of DIC
AML with t(11q23;v); diverse *MLL* fusion genes	Poor	Usually some degree of monocytic differentiation
AML with normal cytogenetics and mutated *NPM*	Favorable	Detected by immunohistochemical staining for NPM
II. AML with MDS-like Features		
With prior MDS	Poor	Diagnosis based on clinical history
AML with multilineage dysplasia	Poor	Maturing cells with dysplastic features typical of MDS
AML with MDS-like cytogenetic aberrations	Poor	Associated with 5q-, 7q-, 20q-aberrations
III. AML, therapy-related	Very poor	If following alkylator therapy or radiation therapy, 2- to 8-year latency period, MDS-like cytogenetic aberrations (e.g., 5q-, 7q-); if following topoisomerase II inhibitor (e.g., etoposide) therapy, 1- to 3-year latency, translocations involving *MLL* (11q23)
IV. AML, Not Otherwise Specified		
AML, minimally differentiated	Intermediate	Negative for myeloperoxidase; myeloid antigens detected on blasts by flow cytometry
AML without maturation	Intermediate	>3% of blasts positive for myeloperoxidase
AML with myelocytic maturation	Intermediate	Full range of myelocytic maturation
AML with myelomonocytic maturation	Intermediate	Myelocytic and monocytic differentiation
AML with monocytic maturation	Intermediate	Nonspecific esterase-positive monoblasts and pro-monocytes predominate in marrow; may see monoblasts or mature monocytes in the blood
AML with erythroid maturation	Intermediate	Erythroid/myeloid subtype defined by >50% dysplastic maturing erythroid precursors and >20% myeloblasts; pure erythroid subtype defined by >80% erythroid precursors without myeloblasts
AML with megakaryocytic maturation	Intermediate	Blasts of megakaryocytic lineage predominate; detected with antibodies against megakaryocyte-specific markers (GPIIb/IIIa or vWF); often associated with marrow fibrosis; most common AML in Down syndrome

AML, Acute myeloid leukemia; DIC, disseminated intravascular coagulation; MDS, myelodysplasia; NPM, nucleophosmin; vWF, von Willebrand factor.

WHO classification of myeloid leukemia

AML with specific cytogenetic abnormalities	AML with t(8;21) (q22;q22) RUNX1-RUNX1T1 CBFα/ETO fusion gene (FAB M2) AML with inv16 (p13;q22) or t(16;16) (p13;q22) CBFβ/MYH11 fusion gene (FAB M4eo) Acute promyelocytic leukemia with t(15;17)(q22;q11-12) PML/RARα fusion gene (FAB M3, M3v) AML with t(9;11)(p21.3;q23.3) MMLT3-KMT2A fusion genes (FAB M4, M5) AML with t(6;9)(p23q34.1) DEK-NUP214 fusion gene AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2) RPN1-EVI1 fusion gene AML with t(1;22)(p13.3;q13.3) RBM15-MKL1 fusion gene (FAB M7) AML with mutated NPM1 AML with mutated CEBPA

WHO classification of myeloid leukemia

AML With multilineage dysplasia With MDS-like cytogenetic abnormalities	With preceding MDS Maturing cells with dysplastic features of MDS 5q-, 7q-, 20q- common
Therapy induced AML	After treatment with alkylating agents (5q-, 7q-) After treatment with epipodophyllotoxin (11q23 MLL)
AML that does not fit above categories Related to Down syndrome	Subclasses defined by extent of differentiation and FAB classification Mixed phenotype acute leukemia with t(9;22)(q34;q11.2) BCR-ABL1 fusion gene Mixed phenotype acute leukemia with t(v;11q23) MLL rearranged Mixed phenotype acute leukemia B/myeloid T/myeloid

FAB classification of myeloid leukemia

Type	Immunophenotype	
M0	CD13+ or CD33+ CD3-, CD14-, CD22-, CD41-, CD61-, CD79- Myeloperoxidase positive	AML with minimal differentiation; immunophenotype distinguishes from ALL
M1	CD13+ or CD33+, CD14- Myeloperoxidase positive	Minimal maturation >3% peroxidase positive
M2	CD13+ or CD33+, CD14- Myeloperoxidase positive	Maturation >3% peroxidase positive Granular cytoplasm
M3	CD13+ or CD33+, CD34-, HLA-DR- Myeloperoxidase positive	Acute promyelocytic leukemia; some Auer rods; 100% peroxidase positive
M4 M4eos		Acute myelomonocytic leukemia (20% monoblasts) with eosinophilia

FAB classification of myeloid leukemia

Type	Immunophenotype	
M5	CD13+ or CD33+, CD14+, HLA-DR- Myeloperoxidase positive Esterase positive	Acute monoblastic or monocytic leukemia
M6	Erythroblasts GlyA+, CD36+ Myeloblasts CD13+ or CD33+, CD14- Myeloperoxidase positive	Acute erythroblastic leukemia (70% erythroblasts)
M7	CD 13-, CD33-, CD41+, CD61+	Acute megakaryoctic leukemia

Acute myeloid leukemia

- 80% of adult leukemias
- 20% of childhood leukemias
- Peaks after 60 years of age
- Anemia, neutropenia, thrombocytopenia secondary to marrow replacement by blasts
- May have gingival hyperplasia (infiltration)
- May have sternal pain (marrow expansion)
- A marrow and/or blood blast count of ≥20% is required to diagnose AML except for rare cases with disease- defining genetic alterations, such as t(8;21)/RUNX1- RUNX1T

Acute myeloid leukemia

- >20% blasts in the bone marrow.
- The most common chromosomal rearrangements are:
- t(8;21)
- Disrupt the CBF1α gene, exhibiting the RUNX1-RUNX1T1 fusion gene
- inv 16 t(16;16)
- CBF1β-MYH11 fusion gene.
- Cells exhibit a partial or complete block in terminal differentiation.

Acute myeloid leukemia

- A deficit of CBF1a/CBF1b activity is not sufficient to cause leukemia.
- Rather, the daughter cells die (failure of hematopoiesis).
- Tyrosine kinase mutation is required in addition to transcription factor mutations to produce acute myeloid leukemia.
- CEBPA mediates lineage specification and differentiation
- 14% cytogenetically normal.

Myeloblasts and a promyelocyte

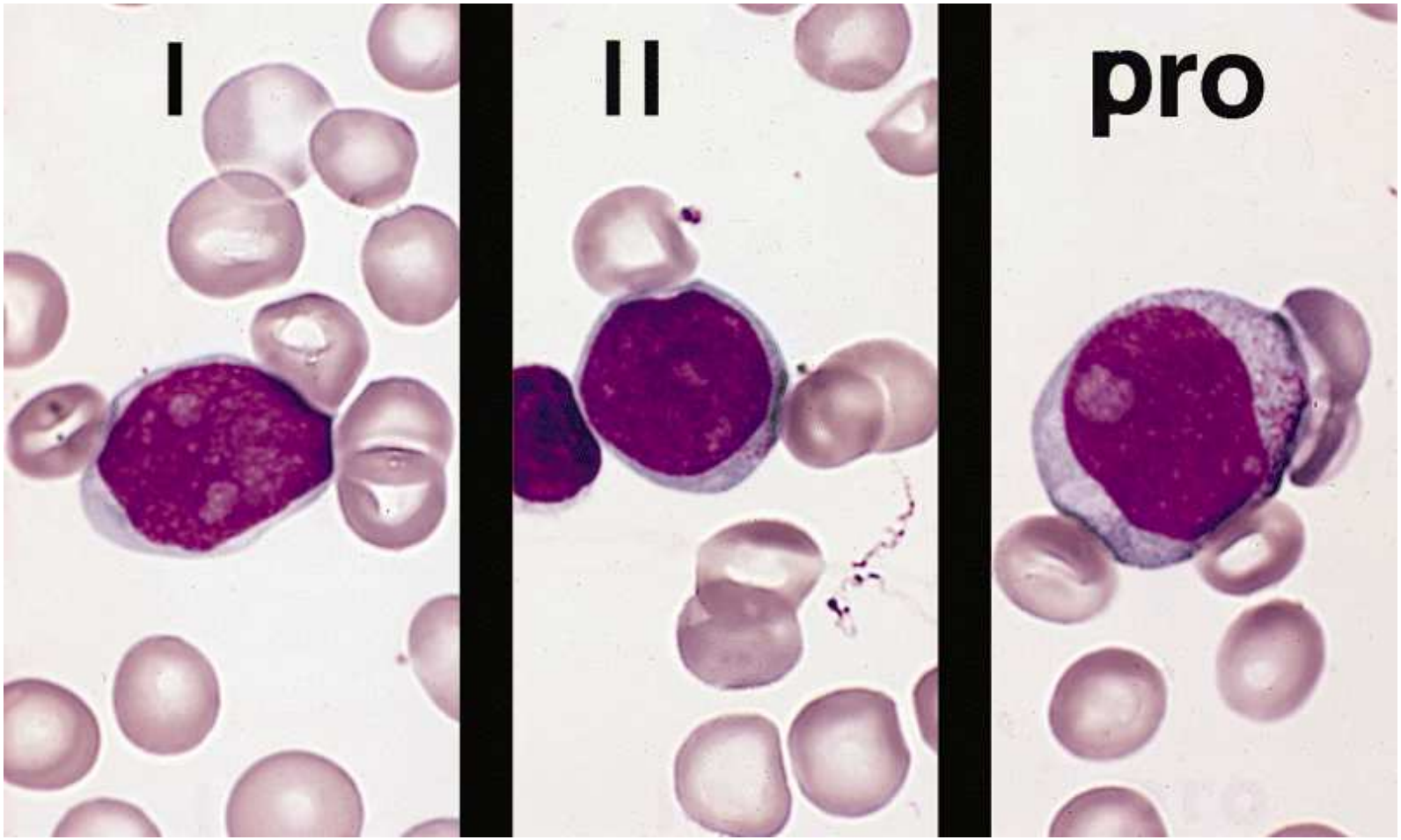


Fig. 23

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

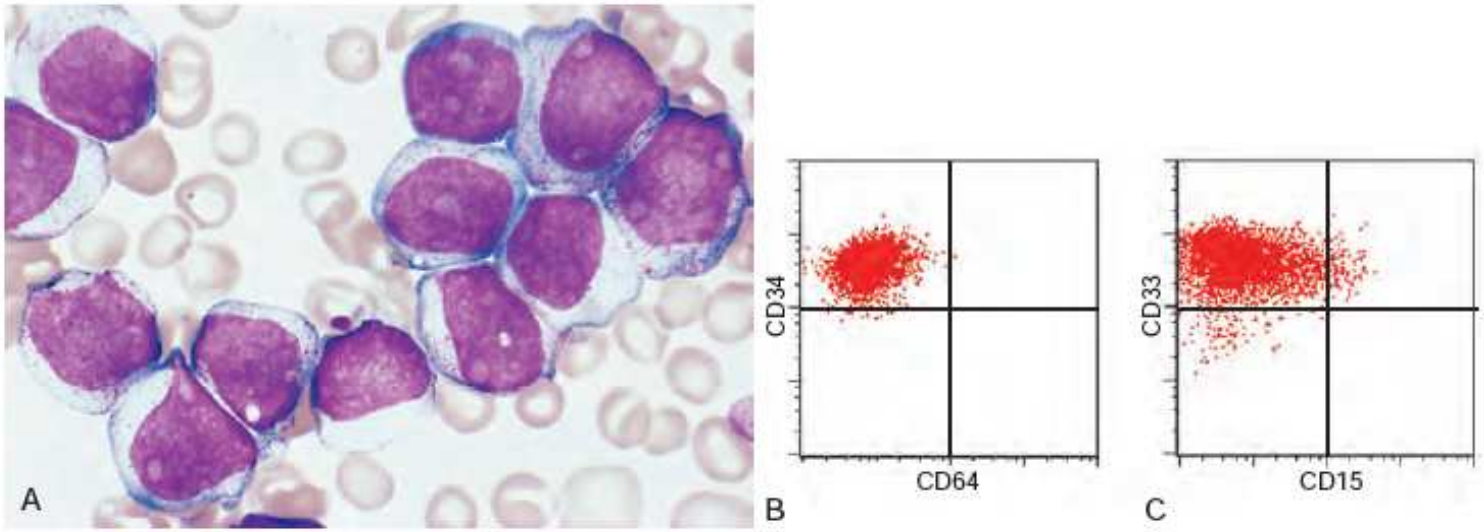


Figure 13-29 **A,** Acute myeloid leukemia without maturation (FAB M1 subtype). Myeloblasts have delicate nuclear chromatin, prominent nucleoli, and fine azurophilic granules in the cytoplasm. **B,** In the flow cytometric analysis shown, the myeloid blasts, represented by the red dots, express CD34, a marker of multipotent stem cells, but do not express CD64, a marker of mature myeloid cells. **C,** The same myeloid blasts express CD33, a marker of immature myeloid cells, and a subset express CD15, a marker of more mature myeloid cells. Thus, these blasts are myeloid cells showing limited maturation. (**A,** Courtesy Dr. Robert W. McKenna Department of Pathology, University of Texas Southwestern Medical School, Dallas, Tex; **B** and **C,** courtesy Dr. Louis Picker, Oregon Health Science Center, Portland, Ore.)

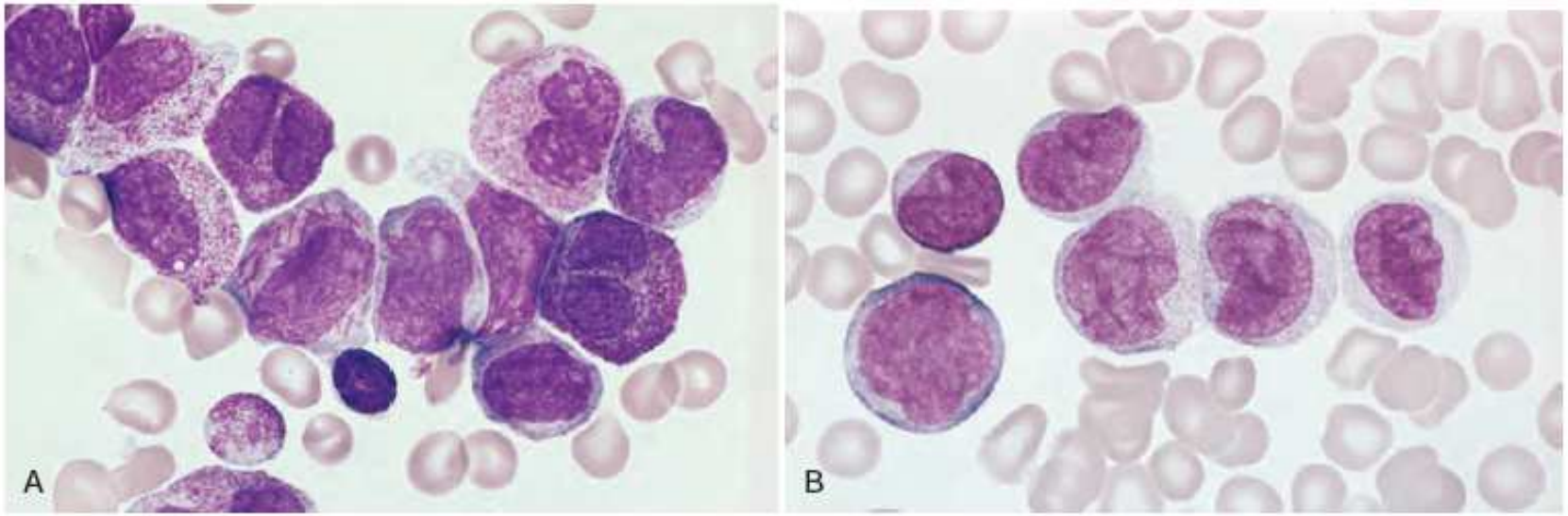
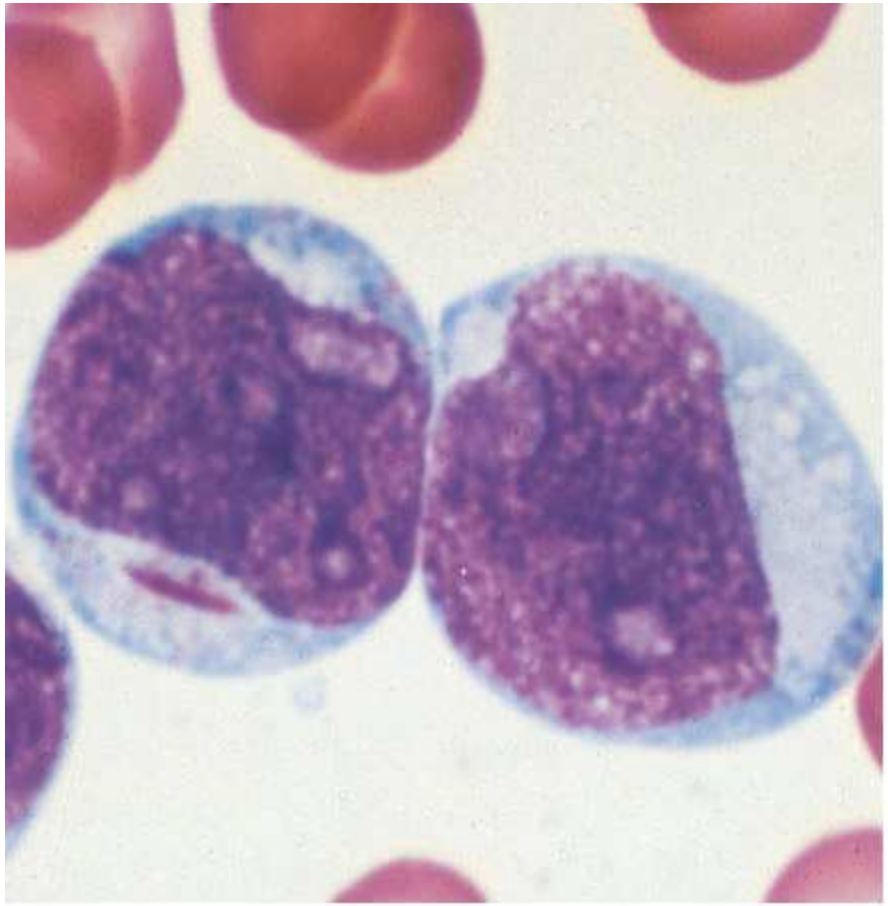


Figure 13-30 Acute myeloid leukemia subtypes. **A,** Acute promyelocytic leukemia with the t(15;17) (FAB M3 subtype). Bone marrow aspirate shows neoplastic promyelocytes with abnormally coarse and numerous azurophilic granules. Other characteristic findings include the presence of several cells with bilobed nuclei and a cell in the center of the field that contains multiple needle-like Auer rods. **B,** Acute myeloid leukemia with monocytic differentiation (FAB M5b subtype). Peripheral smear shows one monoblast and five promonocytes with folded nuclear membranes. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Tex.)

Acute myeloid leukemia.



Leukemic myeloblast with an Auer rod. Multiple large, prominent nucleoli are noted.

Fig. e11-40 Accessed 02/01/2010

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

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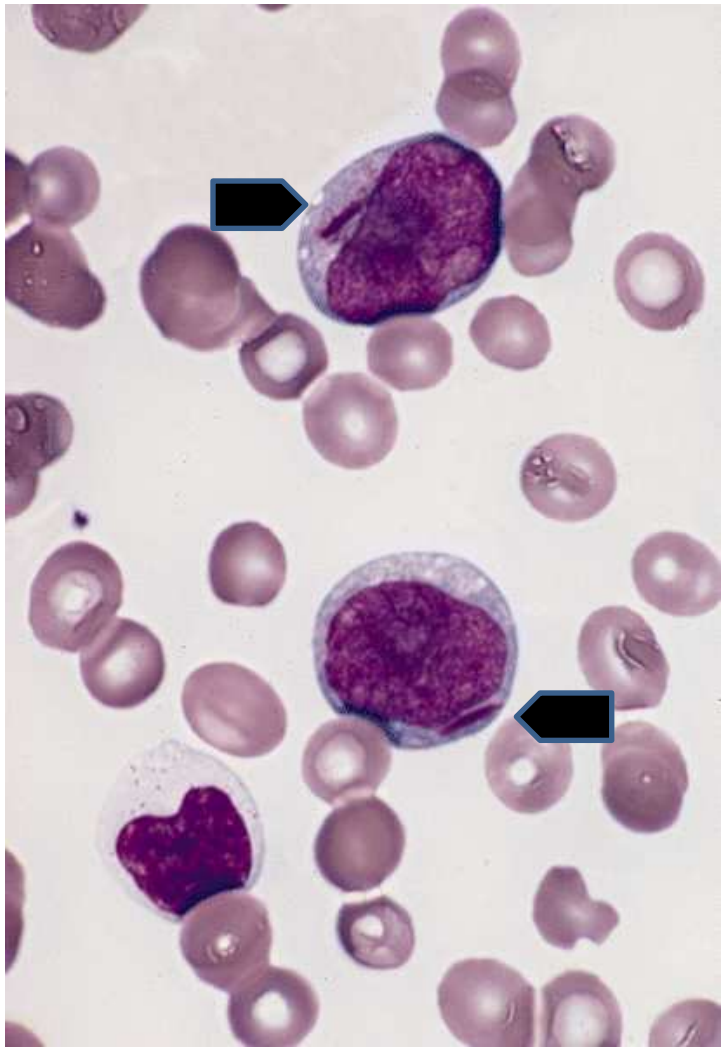
Auer rod



Type I myeloblasts have no granules; type III have many azurophilic granules. These cells are myeloblasts of a patient with acute myelogenous leukemia. These myeloblasts contain Auer rods (arrowheads).

Fig. 26

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Risk status

Core binding factor AML with t(8;21) (q22;q22) PML-RARA subgroup CBFα/ETO fusion gene Core binding factor AML with inv16 (p13;q22) or t(16;16) (p13;q22) CBFB-MYH11 subgroup, without C-KIT mutation Normal cytogenetics with an NPM1 mutation Normal cytogenetics with an isolated CEBPA mutation in the absence of FLT3-ITD	Favorable prognosis
Normal cytogenetics Trisomy 8 (often MDS) t(9;11)(11q23) MLLT3-MLL subgroup t(8;21), inv 16 or t(16;16) with C-KIT mutation Acute promyelocytic leukemia with t(15;17)(q22;q11-12) PML/RARα fusion gene	Intermediate prognosis

Risk status

>3 abnormal clones or monosomal karyotype Del 5, 5q-, del 7, 7q-, p53 mutation t(v,11q23) MLL rearranged Inv 3(q21q26.2) or t(3;3)(q21:q26.2) RPN1-EV11 subgroup Normal cytogenetics with an FLT3/ITD mutation in the absence of an NPM1 mutation t(6;9) (p23:q34) DEK-NUP214 subgroup t(9;22) occurs rarely in AML BAALC	Poor prognosis

Table 8. Cytogenetic and molecular abnormalities defining acute myeloid leukaemia, myelodysplasia-related.

Defining cytogenetic abnormalities
Complex karyotype (≥3 abnormalities)
5q deletion or loss of 5q due to unbalanced translocation
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation
11q deletion
12p deletion or loss of 12p due to unbalanced translocation
Monosomy 13 or 13q deletion
17p deletion or loss of 17p due to unbalanced translocation
Isochromosome 17q
idic(X)(q13)
Defining somatic mutations
ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

Acute myeloid leukaemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with *t(8;21)(q22;q22.1);RUNX1-RUNX1T1*
AML with *inv(16)(p13.1q22)* or *t(16;16)(p13.1;q22);CBFB-MYH11*
APL with *PML-RARA*
AML with *t(9;11)(p21.3;q23.3);MLLT3-KMT2A*
AML with *t(6;9)(p23;q34.1);DEK-NUP214*
AML with *inv(3)(q21.3q26.2)* or *t(3;3)(q21.3;q26.2);GATA2, MECOM*
AML (megakaryoblastic) with *t(1;22)(p13.3;q13.3);RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukaemia
Acute monoblastic/monocytic leukaemia
Pure erythroid leukaemia
Acute megakaryoblastic leukaemia
Acute basophilic leukaemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

APL, Acute promyelocytic leukaemia; NOS, not otherwise specified.

Fig. 2.4

AML

- Alkylating agents and topoisomerase II inhibitors (esp. etoposide) lead to AML at 1%/year
- M1 (myeloid), M2, M4 (myelomonocytic) common
- M4, M5 (monocytic) usually follow etoposide
- t(11;21)
- t(5;17);t(8;21), inv16 favorable
- t(8;21) extramedullary
- M3 (promyelocytic leukemia)
- T(15;17)
- Hyperfibrinolysis in hypergranular M3, M5

AML Risk

- Favorable prognosis
- 45%, normal karyotype
- 30%, NPM1 mutation
- Affects nucleolus and ribosome biogenesis
- Maintenance of genomic stability
- Regulates p53 and ARF
- Loss of tryptophan residues affects nucleolus stability

AML Risk

- 10%, CCAAT/enhanced binding protein α (CEBPA) biallelic mutations
- CEBPA N-terminus frame shift creates a dominant negative, shorter protein
- C-terminus, dysfunctional protein results.
- FLT3 wild type
- FLT3/ITD duplications
- Mixed lineage leukemia (MLL).

AML Risk

- Intermediate prognosis
- FLT3/ITD mutation
- FLT3/ITD mutation negates good risk of NPM1 mutation.
- MLL-PTD positive.
- IDH1 (isocitrate dehydrogenase) mutations (and IDH2) are found in 10% of patients.
- Gain of function
- A negative regulator of TET2 (controls DNA hypo- or hypermethylation).
- t(10;11)) leads to hypermethylation and is associated with better prognosis.

AML Risk

- Poor prognosis
- 10%, p53 mutations
- C-KIT mutation associated with adverse outcomes
- WT1 mutations are noted in 6-7% of cohorts and is associated with short recurrence free interval and survival.
- RUNX1 also associated with negative prognosis.
- Found in myelodysplastic syndrome, radiation induced AML.

AML Risk

- NF1 mutation associated with juvenile myelomonocytic leukemia.
- BAALC (brain and acute leukemia, cytoplasmic)
- ERG (ets-related gene)
- EV1 (ectropic viral integration site)

Acute myeloid leukemia

- Leukemic stem cells have lesser expression of genes associated with proliferation and with cell cycle regulation
- Leukemic stem cells over-express HOPX.
- Permits recruitment of histone decarboxylase activity without the need for direct DNA binding.
- It interacts with multiple pluripotency genes.
- High expression of leukemic stem cell gene signature is of poor prognosis independent of other markers.

Acute myeloid leukemia

- Leukemic stem cells are generally CD34+, CD38-
- Leukemic stem cells are generally CD133+
- Leukemic stem cells generally have a BAALC mutation at 8q22.3
- CLL-1 a lectin like molecule, is an AML stem cell antigen not found on progenitor cells

Immunologic classification of morphologically indistinct leukemia

	B-lymphocyte	**T-lymphocyte**	**Myeloid**
Pathognomonic	Surface IgM+	CD3+ TCR+	MPO+
High likelihood	CD19+ CD20+ CD10+ CD79a+	CD2+ CD5+ CD8+ CD10+	CD17+ CD13+ CD33+ CD65+
Suggestive	TdT CD24+	TdT CD7+ CD1a+ CD79a+	CD14+ CD15+ CD64+

Acute myeloid leukemia

- The most common secondary malignancy in children.
- 11q23 is unfavorable and usually reflects prior epipodyphyllotoxin use
- 80% of children younger than 2 years of age have an M4 or M5 subtype
- 40% if older than 2 years of age
- Monosomy 7 or WBC >100,000/fl is associated with poor response to induction therapy.
- Inv 16 and t(8;21) associated with good response.
- Marrow failure syndromes such as Fanconi's anemia are associated with development of AML.

Acute myeloid leukemia

- 75-85% of children achieve complete remission after induction with an event free survival rate at 5 years of 40%.
- CNS involvement is more common than in ALL and is associated with M4 and M5 subtypes and inv 16 or t(9;11)11q23 abnormalities.

Table 6. Diagnostic criteria of chronic myelomonocytic leukaemia.

Prerequisite criteria
1. Persistent absolute ($\geq 0.5 \times 10^9$/L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]
Supporting criteria
1. Dysplasia involving ≥1 myeloid lineages.[d]
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.[e]
Requirements for diagnosis
- Pre-requisite criteria must be present in all cases.
- If monocytosis is $\geq 1 \times 10^9$/L: one or more supporting criteria must be met.
- If monocytosis is ≥0.5 and $<1 \times 10^9$/L: supporting criteria 1 and 2 must be met.
Subtyping criteria
- Myelodysplastic CMML (MD-CMML): WBC $< 13 \times 10^9$/L
- Myeloproliferative CMML (MP-CMML): WBC $\geq 13 \times 10^9$/L
Subgrouping criteria (based on percentage of blasts and promonocytes)
CMML-1: <5% in peripheral blood and <10% in bone marrow
CMML-2: 5–19% in peripheral blood and 10-19% in bone marrow

[a]Blasts and blast equivalents include myeloblasts, monoblasts and promonocytes.

[b]Myeloproliferative neoplasms (MPN) can be associated with monocytosis at presentation or during the course of the disease; such cases can mimic CMML. In these instances, a documented history of MPN excludes CMML. The presence of MPN features in the bone marrow and/or high burden of MPN-associated mutations (*JAK2, CALR* or *MPL*) tends to support MPN with monocytosis rather than CMML.

[c]Criteria for myeloid/lymphoid neoplasms with tyrosine kinase fusions should be specifically excluded in cases with eosinophilia.

[d]Morphologic dysplasia should be present in ≥10% of cells of a haematopoietic lineage in the bone marrow.

[e]Based on detection of increased classical monocytes (>94%) in the absence of known active autoimmune diseases and/or systemic inflammatory syndromes.

Juvenile myelomonocytic leukemia

- JMML is an MDS/MPN of infancy characterized by granulomonocytic expansion and dismal prognosis without treatment (median survival 10–12 months).
- Somatic or germline mutations in RAS pathway genes are found in >90% of cases.
- Diagnostic criteria include: peripheral blood (PB) monocy tes >10^9/L, splenomegaly and either a somatic mutation in PTPN11, NF1, CBL, KRAS

Juvenile myelomonocytic leukemia

- OR
- NRAS or two of the following criteria: increased haemoglobin F, erythromyeloid precursors on PB smear, GM-CSF hypersensitivity in colony assays or STAT5 hyperphosphorylation.
- Allogenic stem cell transplant is curative

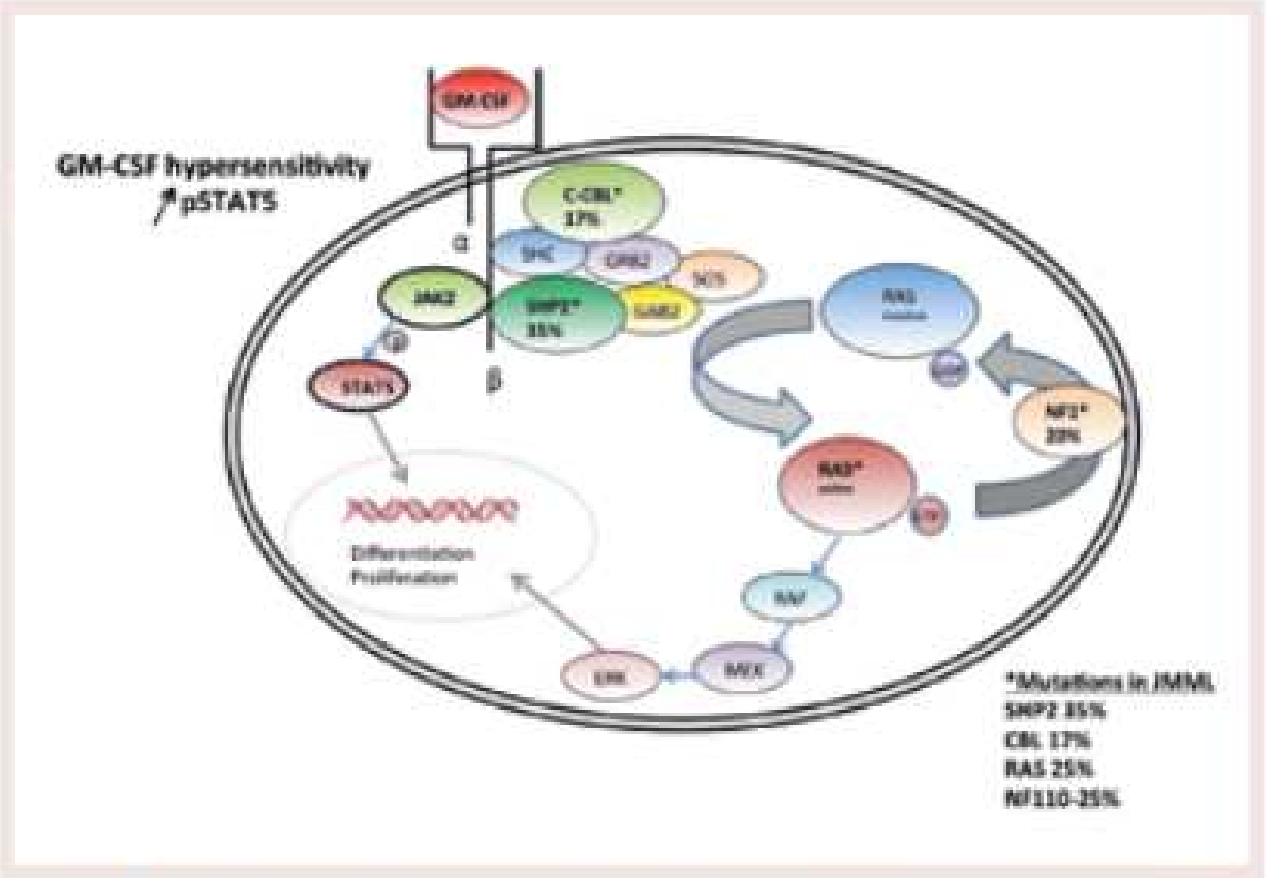


Fig. 15.7

GM-CSF, Granulocyte–macrophage colony-stimulating factor; JMML, juvenile myelomonocytic leukaemia.

Criteria	CMML	JMML	aCML	MDS/MPN-RS-T
Age (years)	~72	<14	~70	~72
Monocytes (x 10^9/L)	>1 (>10% WBCs)	>1	<1 (<10% WBCs)	-
Myelaemia (%)	<10%	Present	>10%	-
WBCs (x 10^9/L)	-	-	>13	-
Platelets (x 10^9/L)	-	-	-	>450
Ring sideroblasts >15%	No	No	No	Yes
Medullary/peripheral blasts (%)	<20%	<20%	<20%	<20%
Dysplasia	≥1	Minimal	Dysgranulopoiesis	≥1
BCR-ABL1, *PDGFRA/B*, *FGFR1*, *PCM1-JAK2* rearrangements	No	No	No	No

Fig. 15.2

aCML, Atypical chronic myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; JMML, juvenile myelomonocytic leukaemia; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; MDS/MPN-RS-T, MDS/MPN with ring sideroblasts and thrombocytosis; WBC, white blood cell.

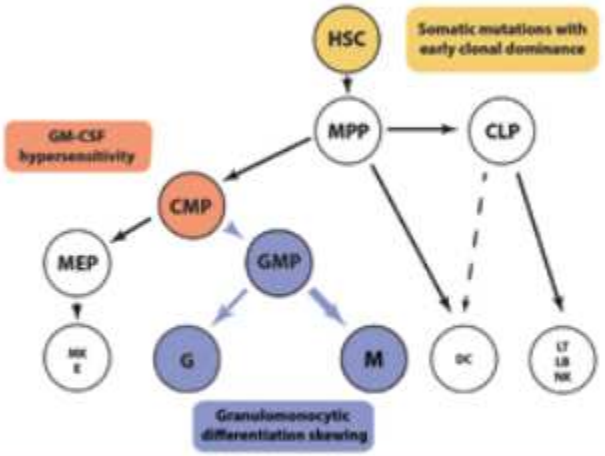


Fig. 15.3

CLP, Common lymphoid progenitor; CMML, chronic myelomonocytic leukaemia; CMP, common myeloid progenitor; DC, dendritic cell; E, erythrocyte; G, granulocyte; GM-CSF, granulocyte–macrophage colony-stimulating factor; GMP, granulocyte monocyte progenitor; HSC, haematopoietic stem cell; LB, B lymphocyte; LT, T lymphocyte; M, monocyte; MEP, megakaryocyte erythrocyte progenitor; MK, megakaryocyte; MPP, multipotent progenitor; NK natural killer.

Acute promyelocytic leukemia

- t(15,17) abnormality.
- Retinoic acid receptor-a (RARα) normally activates transcription, but when fused to PML, it is converted to a repressor that turns off genes required for full and complete myeloid differentiation.
- All trans retinoic acid (ATRA) acts as a differentiator (promotes myotubule formation) and is used in therapy.

Acute promyelocytic leukemia

- Also frequently acquire point mutations in FLT3, a tyrosine kinase, that result in its constitutive activation
- Synergize with the block in differentiation produced by the RARα-PML fusion protein.

Acute promyelocytic leukemia

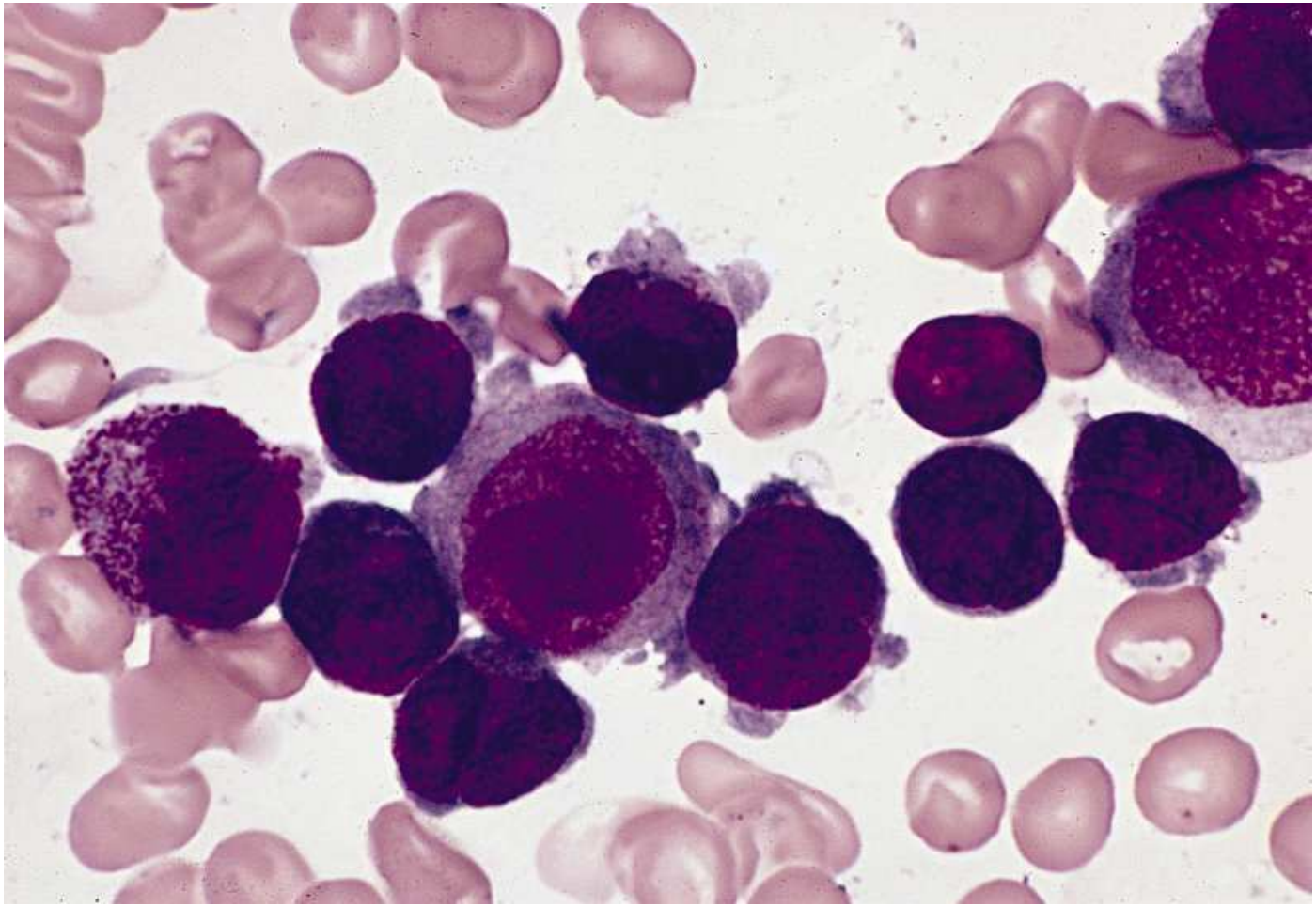
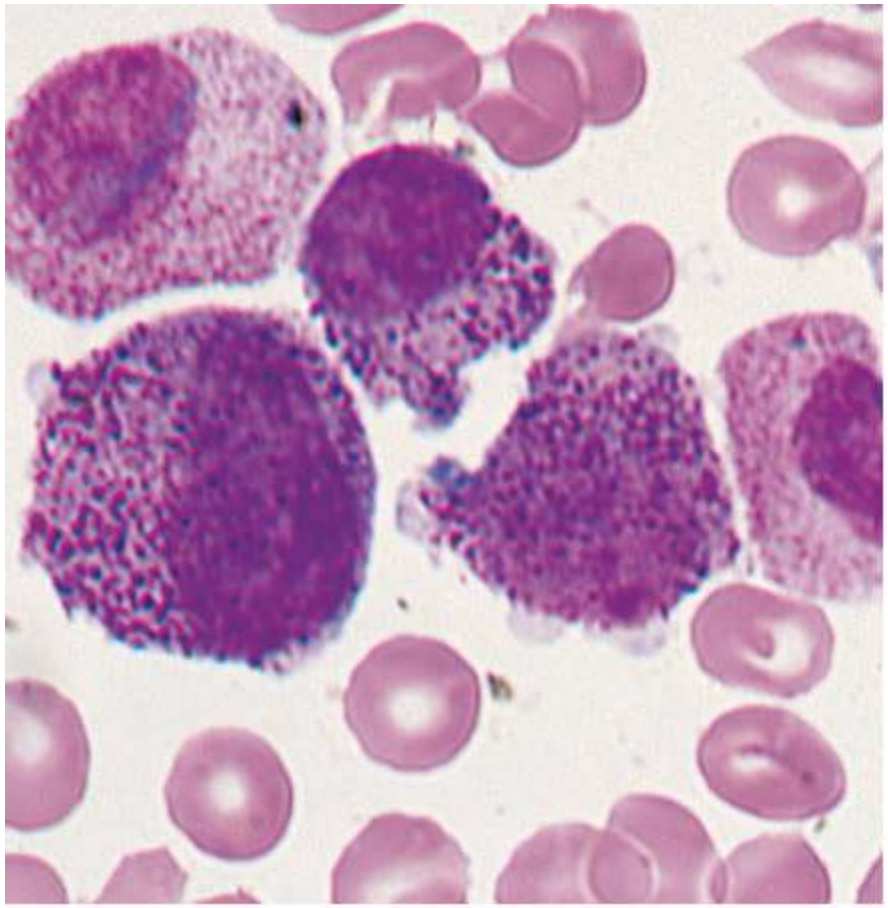


Fig. 49

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Acute promyelocytic leukemia



Prominent cytoplasmic granules are present in the leukemia cells.

Fig. e11-11 Accessed 02/01/2010

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

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Acute myelomonocytic leukemia

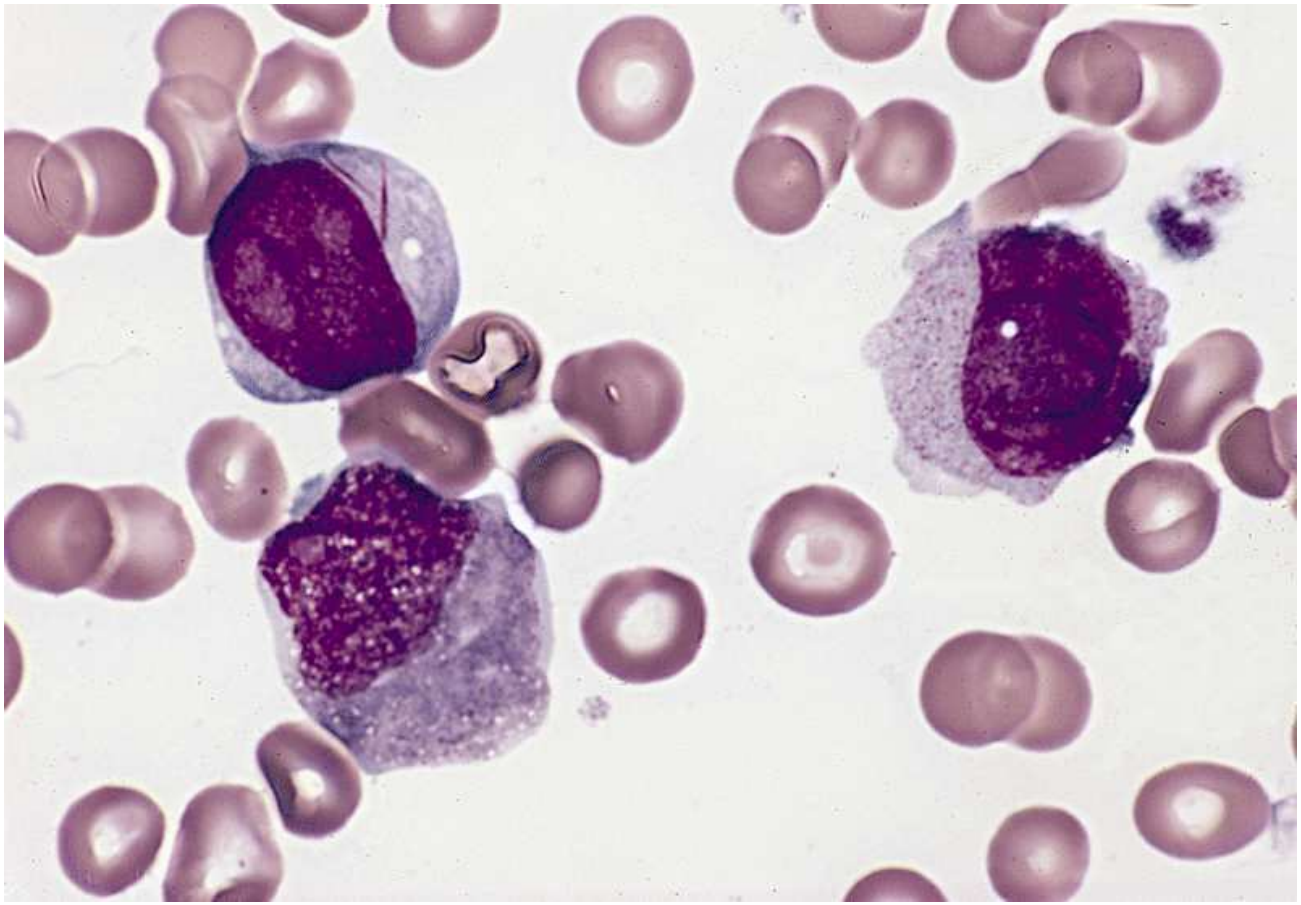


Fig. 57

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Acute monoblastic leukemia

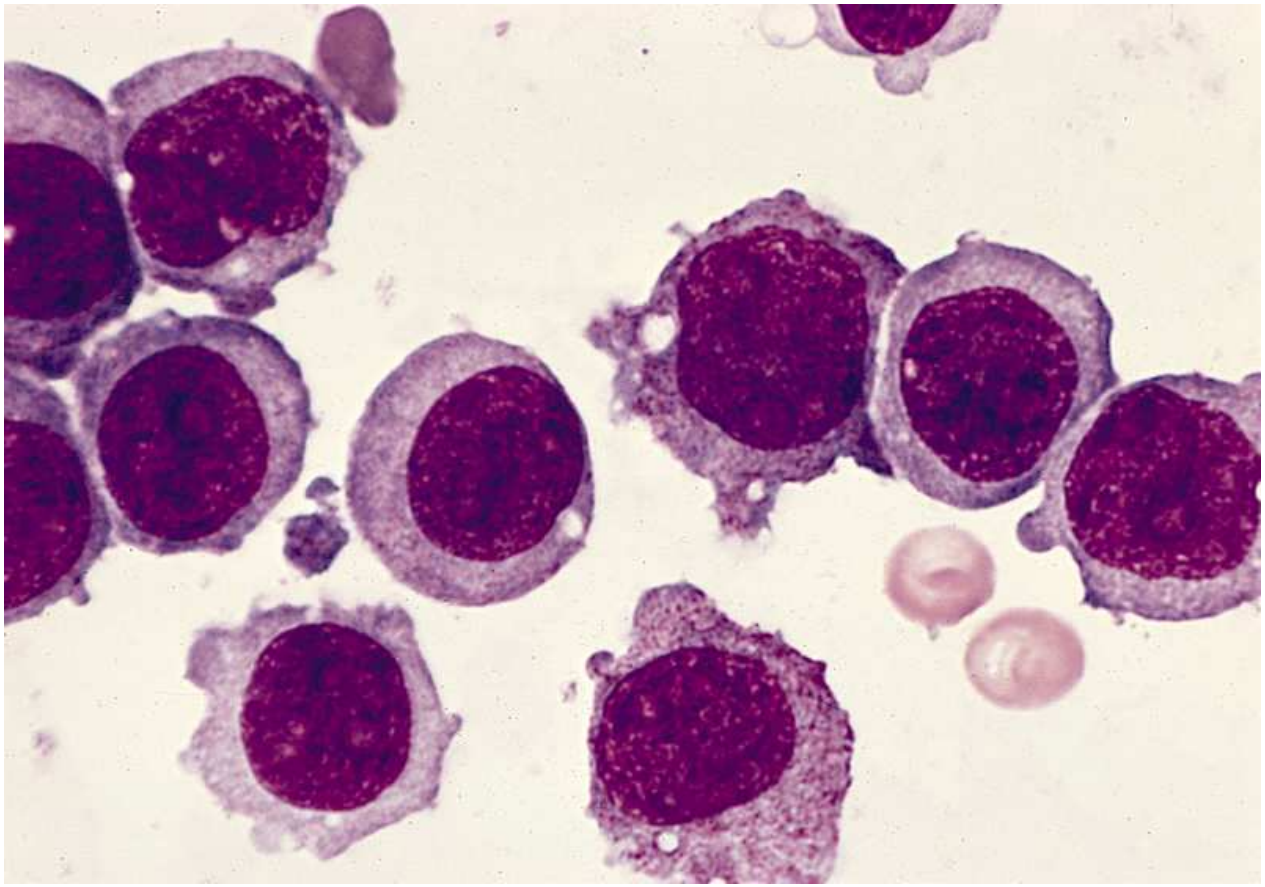


Fig. 67

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Acute basophilic leukemia

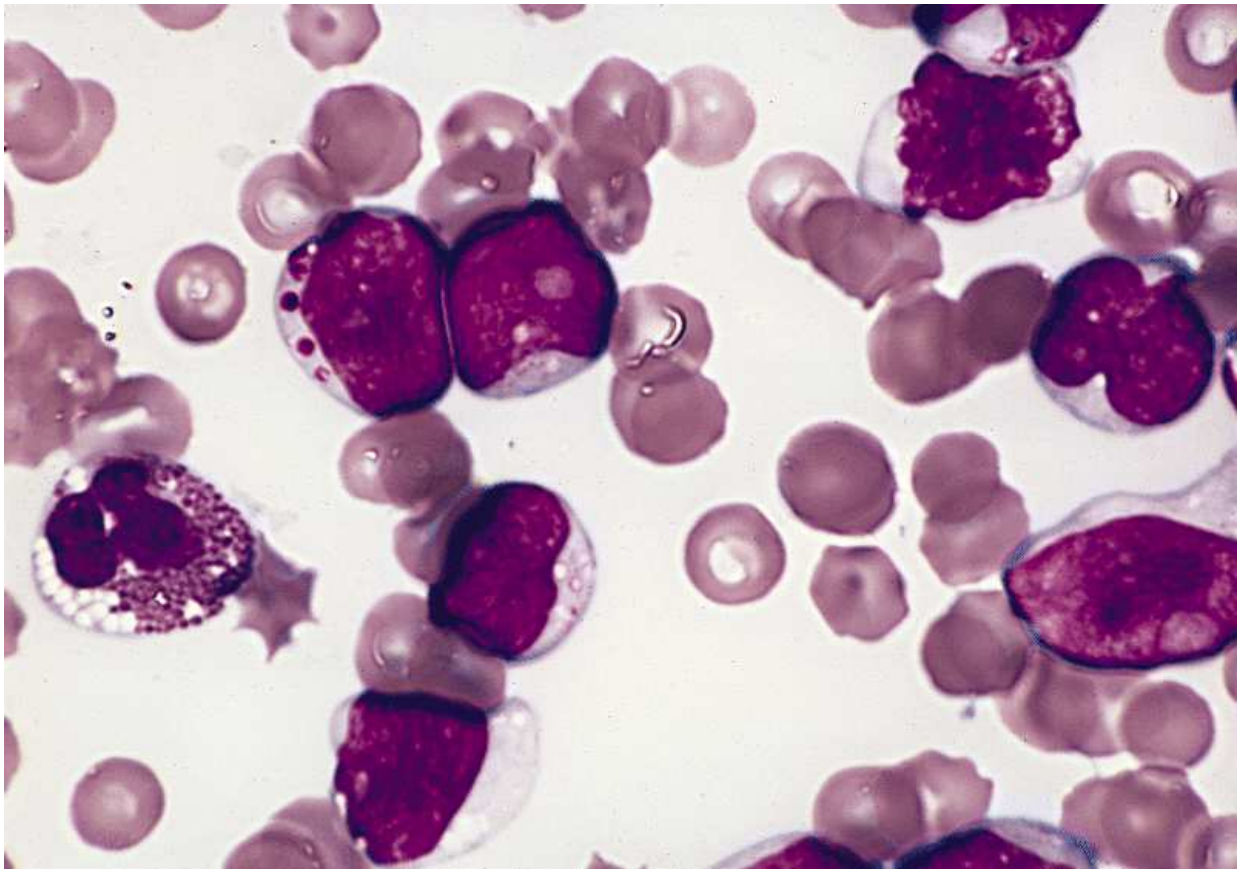
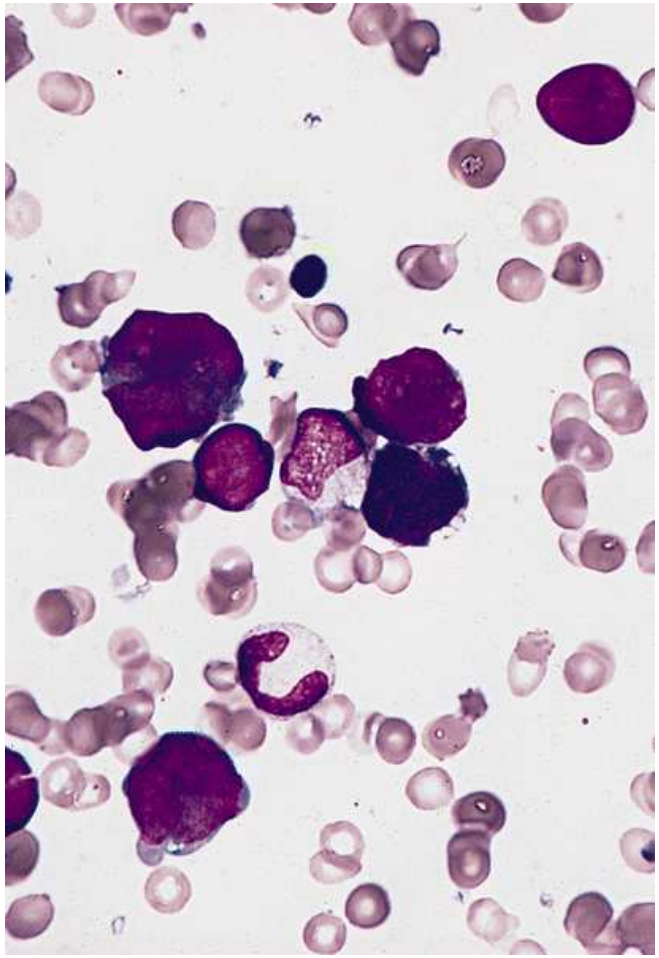


Fig. 99

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Acute megakaryoblastic leukemia



Bone marrow smear from a 14-month-old child containing large blasts and promegakaryocytes. The promegakaryocytes are larger than the blasts and have a coarse nuclear chromatin and irregularly shaped nuclei; cytoplasmic budding is present. Neutrophil precursors are present. (Wright-Giemsa stain).

Fig. 92 A

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

AML with dysplasia

- The WHO classification gives a special place to AML with dysplasia in two to three cell series, either as primary syndrome or following a myelodysplastic syndrome or a myeloproliferative disease .
- Criteria for dysgranulopoiesis:
- >50% of all segmented neutrophils have no granules or very few granules, or show the Pelger-Hüet anomaly, or are peroxidase-negative.

AML with dysplasia

- Criteria for dyserythropoiesis:
- >50% of the red cell precursor cells display one of the following anomalies: karyorrhexis, megaloblastoid traits, more than one nucleus, nuclear fragmentation.
- Criteria for dysmegakaryopoiesis:
- >50% of at least six megakaryocytes show one of the following anomalies: micromegakaryocytes, more than one separate nucleus, large mononuclear cells.

.

Hypoplastic AML

- There are times in the “aleukemic” leukemias of the FAB or WHO classifications, where the bone marrow is largely empty and shows only a few blasts, which usually occur in clusters.
- In such a case, a very detailed analysis is essential for a differential diagnosis of aleukemic leukemia as opposed to aplastic anemia.

Transient myeloproliferative disorder of Down's syndrome

- Affects 10% of newborns with Down's syndrome.
- Rarely occurs with trisomy 21 without Down's syndrome.
- Resembles congenital acute leukemia
- Occurs within first days of life with numerous blasts in peripheral blood, more than in marrow
- Usually resolves in 2-14 weeks in neonates
- 20-30% progress to AML-M7/AMKL within 3 years.
- Early death in 17%
- Associated with hepatic fibrosis

Transient myeloproliferative disorder of Down's syndrome

- Mutations in GATA1 gene in almost all cases (compared to 4% of all Down's syndrome infants).
- Loss of GATA1 impairs maturation of megakaryocyte and erythroid progenitors.
- Specific mutations may differ in TMD and subsequent AML-M7/AMKL
- JAK3 mutations found in 50%.
- JAK1 mutations found in those Down's patients who develop lymphoblastic leukemia.
- Reacts with STAT. Stimulates IL-2, 4, 10 receptor families.
- CD41 (100%), CD45 (100%); also CD7 (93%), CD34 (89%), HLA-DR (80%)

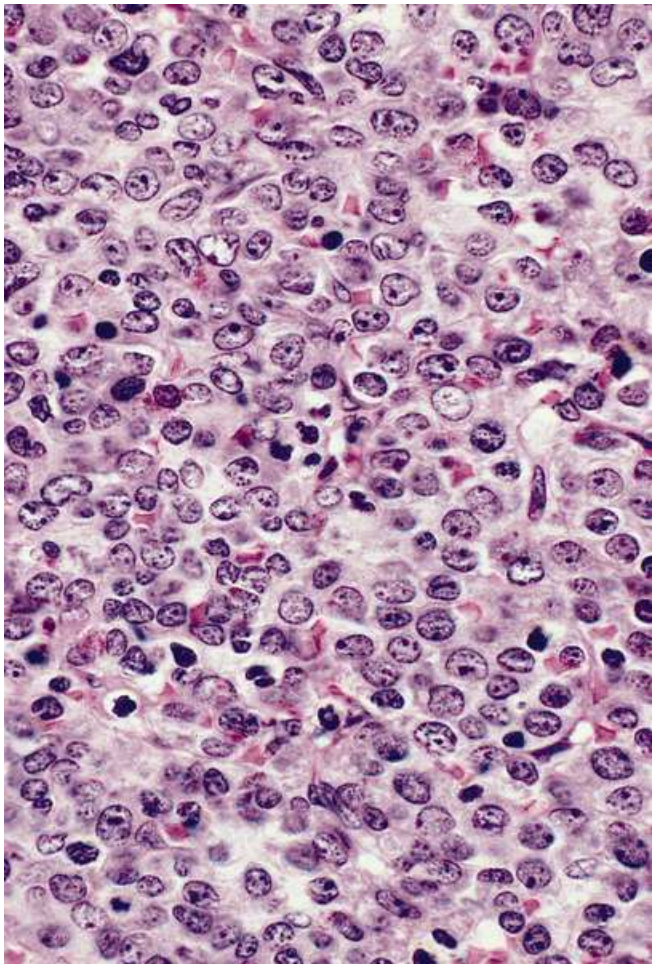
Chronic myeloid leukemia

- The common attributes of chronic myeloproliferative diseases are onset in middle age, fatigue, development of splenomegaly, and slow disease progression.
- 95% t(9;22)
- Philadelphia chromosome
- BCR-ABL translocation
- 5-6 year survival in chronic phase
- <1 year in accelerated phase
- <6 months in blast phase

Chronic myeloid leukemia

- Accelerated Phase
- Bone marrow or peripheral blood blasts of 10%-19%
- Peripheral blood basophils >20%
- bcr rearrangement
- Blast phase (“crisis”)
- Bone marrow or peripheral blood blasts greater than or equal to 20%
- Myeloid sarcoma
- Presence of lymphoblasts (>5%) suggesting lymphoblastic crisis

Myeloid sarcoma



Lymph node-associated mass from the anterior cervical region of a 7-year-old boy. Most of the cells are immature, with round to oval nuclei with distinct, relatively prominent, eosinophilic nucleoli. The majority of cells have moderate to abundant cytoplasm. Several immature eosinophils are present. (Hematoxylin and eosin stain).

Fig. 111 A

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

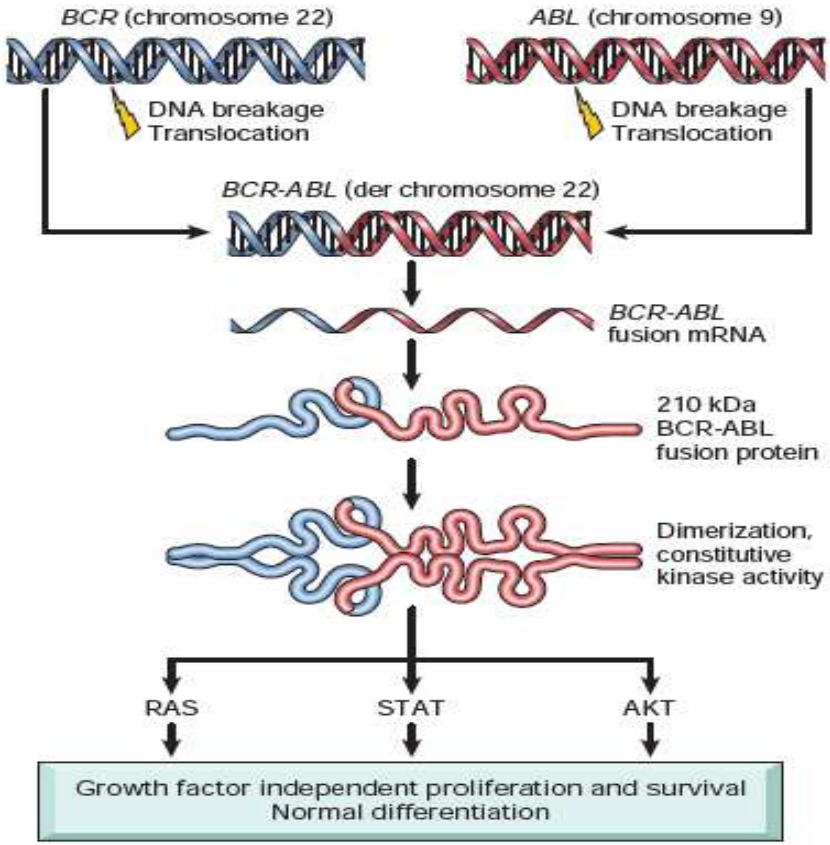
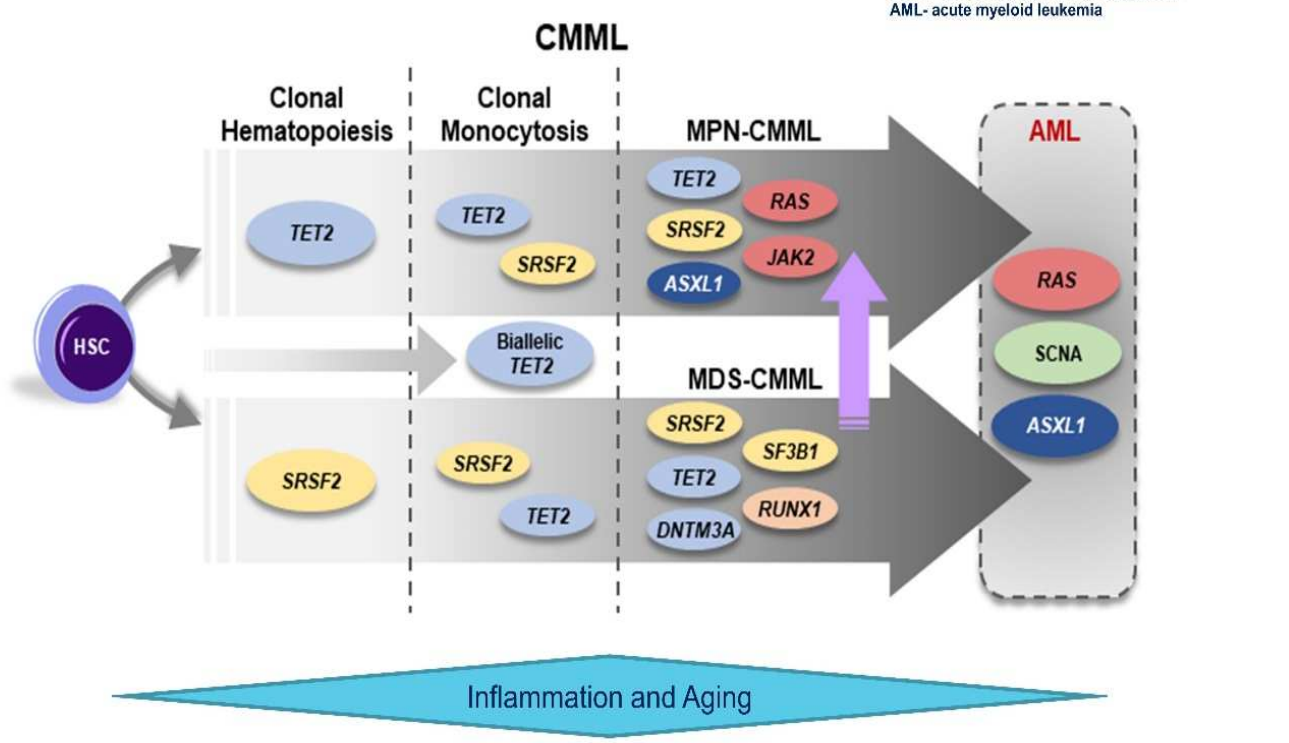


Figure 13-32 Pathogenesis of chronic myeloid leukemia. Breakage and joining of *BCR* and *ABL* creates a chimeric *BCR-ABL* fusion gene that encodes a constitutively active BCR-ABL tyrosine kinase. BCR-ABL activates multiple downstream pathways, which drive growth factor-independent proliferation and survival of bone marrow progenitors. Because BCR-ABL does not interfere with differentiation, the net result is an increase in mature elements in the peripheral blood, particularly granulocytes and platelets.

CMML – Clonal Evolution

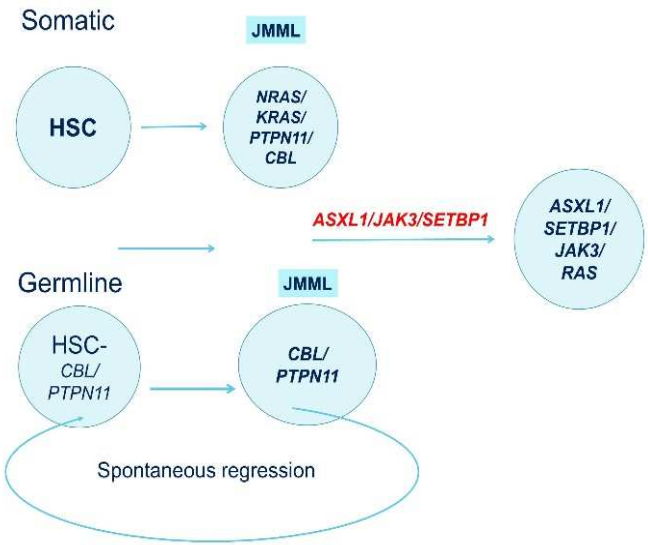
CMML- chronic myelomonocytic leukemia
MPN- myeloproliferative neoplasm
MDS- myelodysplastic syndrome
SCNA- somatic copy number alterations
AML- acute myeloid leukemia



Emanuel PD et al. *Leukemia* 2008
Niemeyer C et al. *Blood* 2018

JMML Genetics- *RAS*(opathy)

Gene	Site of Mutation	Frequency
PTPN11	E76K, D61Y, D61V, E69K, A72V, A72T, E76V/G/A	35%
RAS *KRAS* *NRAS* *HRAS*	 Codons 12 & 13 Codon 13	 25%
NF-1	Loss of wild type allele	11-15%
CBL	Codons 371, 380, 381, 384, 396, 398, 404 and 408 Splice sites 1227, 1228 and 1096.	17%



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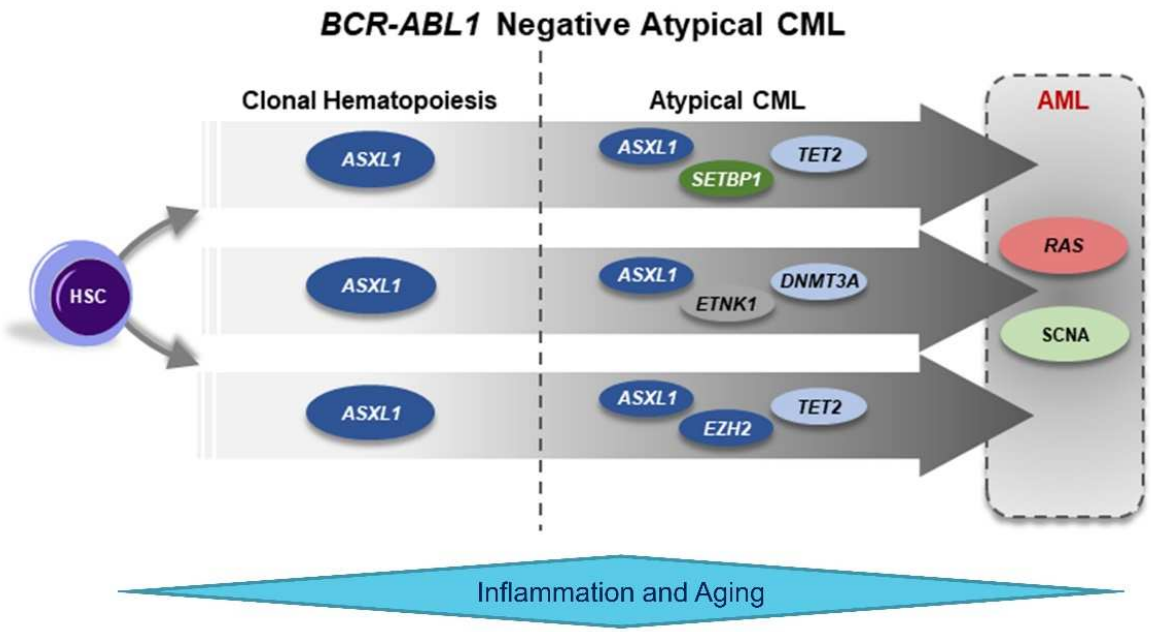
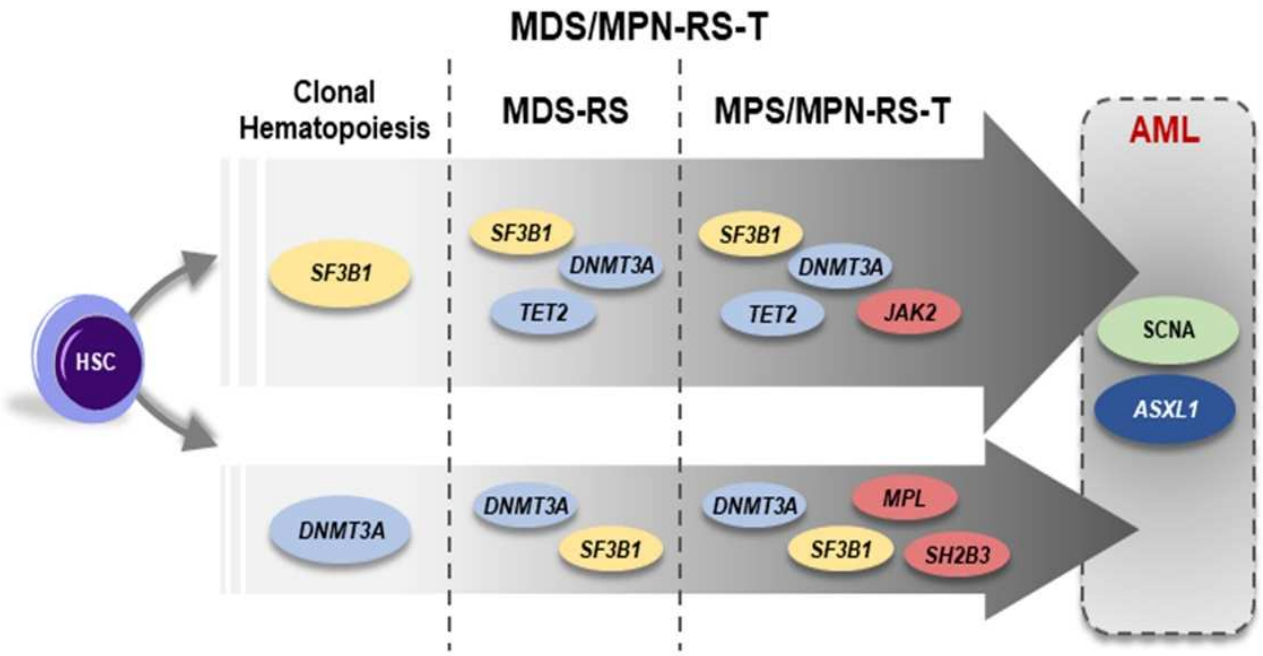

BCR-ABL1 Negative Atypical CML
Clonal Hematopoiesis
Atypical CML
AML
HSC
ASXL1
ASXL1
TET2
SETBP1
ASXL1
ASXL1
DNMT3A
ETNK1
ASXL1
ASXL1
TET2
EZH2
RAS
SCNA
Inflammation and Aging


MDS/MPN-RS-T
Clonal Hematopoiesis
MDS-RS
MPS/MPN-RS-T
AML
HSC
SF3B1
SF3B1
DNMT3A
TET2
SF3B1
DNMT3A
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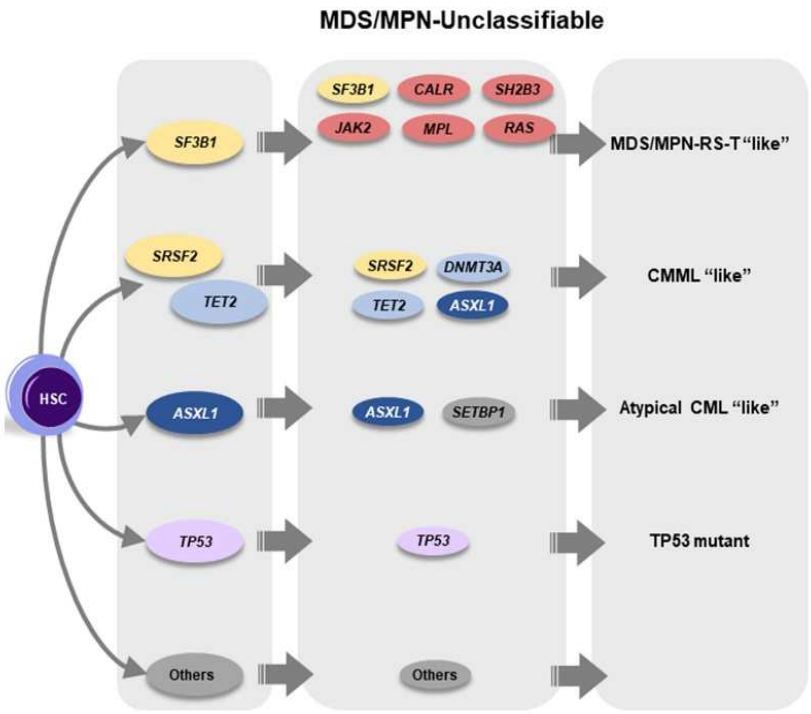
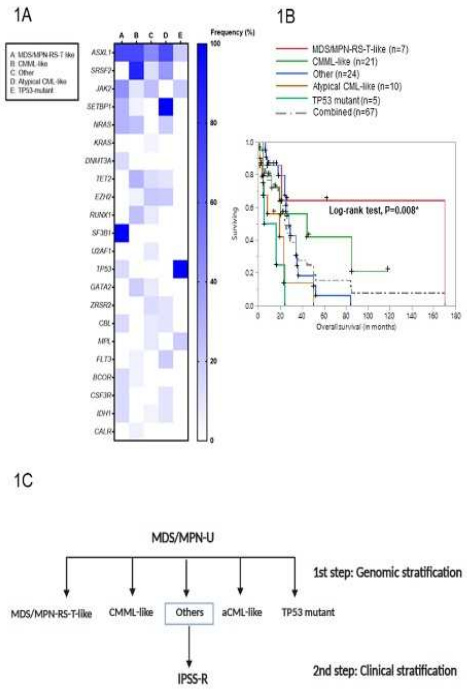
DNMT3A
MPL
SF3B1
SH2B3





Mangaonkar & Patnaik et al *Leukemia* 2021

Table 13. Lineage assignment criteria for mixed-phenotype acute leukaemia.

	Criterion
B lineage	
CD19 strong[a]	1 or more also strongly expressed: CD10, CD22, or CD79a[c]
or,	
CD19 weak[b]	2 or more also strongly expressed: CD10, CD22, or CD79a[c]
T lineage	
CD3 (cytoplasmic or surface)[d]	Intensity in part exceeds 50% of mature T-cells level by flow cytometry or, Immunocytochemistry positive with non-zeta chain reagent
Myeloid lineage	
Myeloperoxidase	Intensity in part exceeds 50% of mature neutrophil level
or,	
Monocytic differentiation	2 or more expressed: Non-specific esterase, CD11c, CD14, CD64 or lysozyme

[a]CD19 intensity in part exceeds 50% of normal B cell progenitor by flow cytometry.
[b]CD19 intensity does not exceed 50% of normal B cell progenitor by flow cytometry.
[c]Provided T lineage not under consideration, otherwise cannot use CD79a.
[d]Using anti-CD3 epsilon chain antibody.

Table 12. Acute leukaemias of ambiguous lineage.

Acute leukaemia of ambiguous lineage with defining genetic abnormalities
Mixed-phenotype acute leukaemia with *BCR::ABL1* fusion
Mixed-phenotype acute leukaemia with *KMT2A* rearrangement
Acute leukaemia of ambiguous lineage with other defined genetic alterations
Mixed-phenotype acute leukaemia with *ZNF384* rearrangement
Acute leukaemia of ambiguous lineage with *BCL11B* rearrangement
Acute leukaemia of ambiguous lineage, immunophenotypically defined
Mixed-phenotype acute leukaemia, B/myeloid
Mixed-phenotype acute leukaemia, T/myeloid
Mixed-phenotype acute leukaemia, rare types
Acute leukaemia of ambiguous lineage, not otherwise specified
Acute undifferentiated leukaemia

Table 13-11 Tyrosine Kinase Mutations in Myeloproliferative Disorders

Disorder	Mutation	Frequency*	Consequences†
Chronic myelogenous leukemia	*BCR-ABL* fusion gene	100%	Constitutive ABL kinase activation‡
Polycythemia vera	*JAK2* point mutations	>95%	Constitutive JAK2 kinase activation
Essential thrombocythemia	*JAK2* point mutations *MPL* point mutations	50% to 60% 5% to 10%	Constitutive JAK2 kinase activation Constitutive MPL kinase activation
Primary myelofibrosis	*JAK2* point mutations *MPL* point mutations	50% to 60% 5% to 10%	Constitutive JAK2 kinase activation Constitutive MPL kinase activation
Systemic mastocytosis	*KIT* point mutations	>90%	Constitutive KIT kinase activation
Chronic eosinophilic leukemia§	*FIP1L1-PDGFRA* fusion gene *PDE4DIP-PDGFRB* fusion gene	Common Rare	Constitutive PDGFRα kinase activation Constitutive PDGFRβ kinase activation‡
Stem cell leukemia‖	Various *FGFR1* fusion genes	100%	Constitutive FGFR1 kinase activation¶

*Refers to frequency within a diagnostic category.
†All stimulate ligand-independent pro-growth and survival signals.
‡Responds to imatinib therapy.
§Associated with Loeffler endocarditis (Chapter 12).
‖Rare disorder originating in pluripotent hematopoietic stem cells that presents with concomitant myeloproliferative disorder and lymphoblastic leukemia/lymphoma.
¶Responds to PKC412 therapy.

Table 11. Genetic abnormalities defining myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions.

PDGFRA rearrangement
PDGFRB rearrangement
FGFR1 rearrangement
JAK2 rearrangement
FLT3 rearrangement
ETV6::ABL1 fusion
Other defined tyrosine kinase fusions:
ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; FGFR1OP::RET

Table 14. Dendritic cell and histiocytic neoplasms.

Plasmacytoid dendritic cell neoplasms
Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
Blastic plasmacytoid dendritic cell neoplasm
Langerhans cell and other dendritic cell neoplasms
Langerhans cells neoplasms
Langerhans cell histiocytosis
Langerhans cell sarcoma
Other dendritic cell neoplasms
Indeterminate dendritic cell tumour
Interdigitating dendritic cell sarcoma
Histiocytic neoplasms
Juvenile xanthogranuloma
Erdheim-Chester disease
Rosai-Dorfman disease
ALK-positive histiocytosis
Histiocytic sarcoma

Table 15. Immunophenotypic diagnostic criteria of blastic plasmacytoid dendritic cell neoplasm.

Expected positive expression:
CD123*
TCF4*
TCL1*
CD303 *
CD304*
CD4
CD56
Expected negative markers:
CD3
CD14
CD19
CD34
Lysozyme
Myeloperoxidase
Immunophenotypic diagnostic criteria:
-Expression of CD123 and one other pDC marker(*) in addition to CD4 and/or CD56.
or,
-Expression of any three pDC markers and absent expression of all expected negative markers.

Chronic myeloproliferative disorders

- Tyrosine kinase abnormalities:
- CML manifests BCR-ABL fusion gene
- Polycythemia vera manifests JAK2 mutation
- Essential thrombocythemia and primary myelofibrosis manifest JAK2 or MPL mutations
- Systemic mastocytosis manifests c-kit mutations
- Chronic eosinophilic leukemia commonly manifests FIP1L-PDGFRα fusion gene
- Rarely, PDE4DIP-PDGFRβ fusion gene
- Stem cell leukemia manifests FGRF1 fusion genes

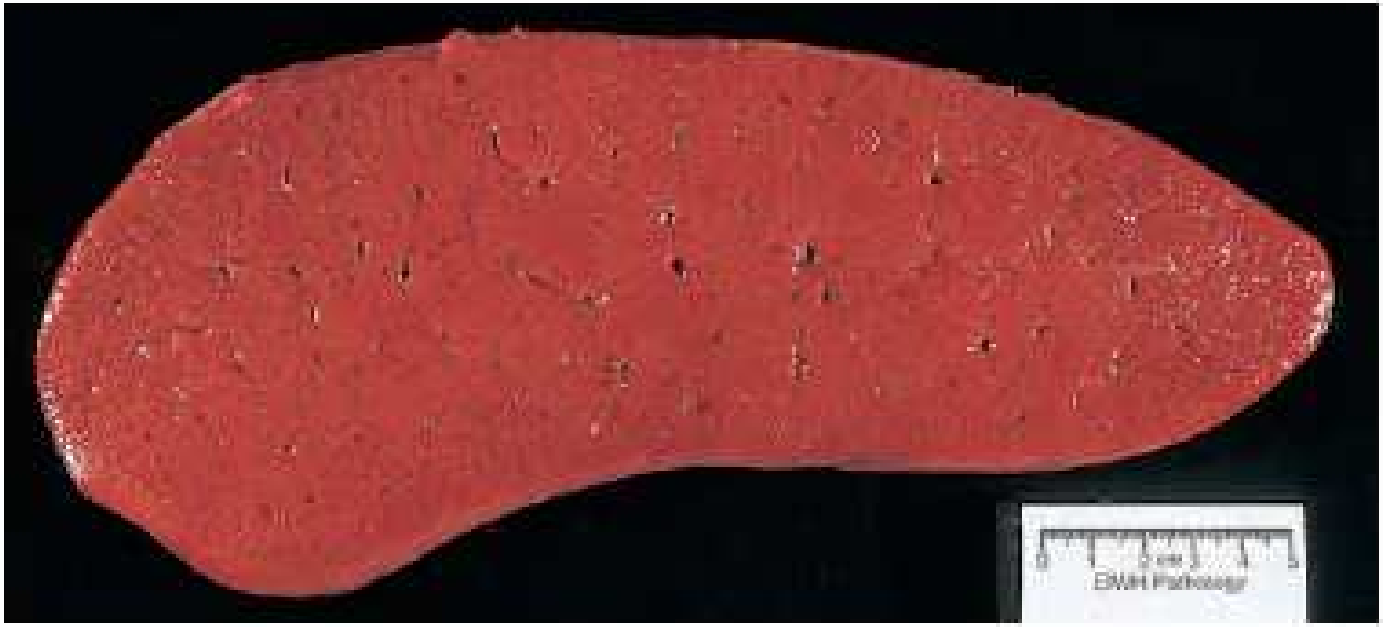


Figure 13-34 Chronic myeloid leukemia (spleen). Enlarged spleen (2630 gm; normal: 150 to 200 gm) with greatly expanded red pulp stemming from neoplastic hematopoiesis. (Courtesy Dr. Daniel Jones, Department of Pathology, MD Anderson Cancer Center, Houston, Tex.)

Chronic myeloid leukemia

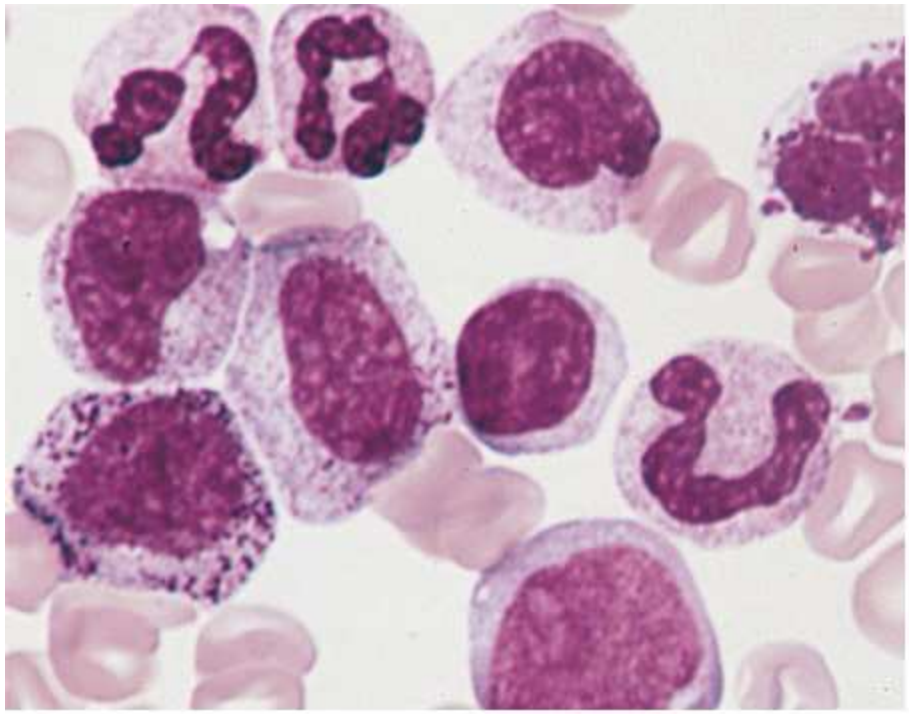


Fig. e11-45 Accessed 02/01/2010

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

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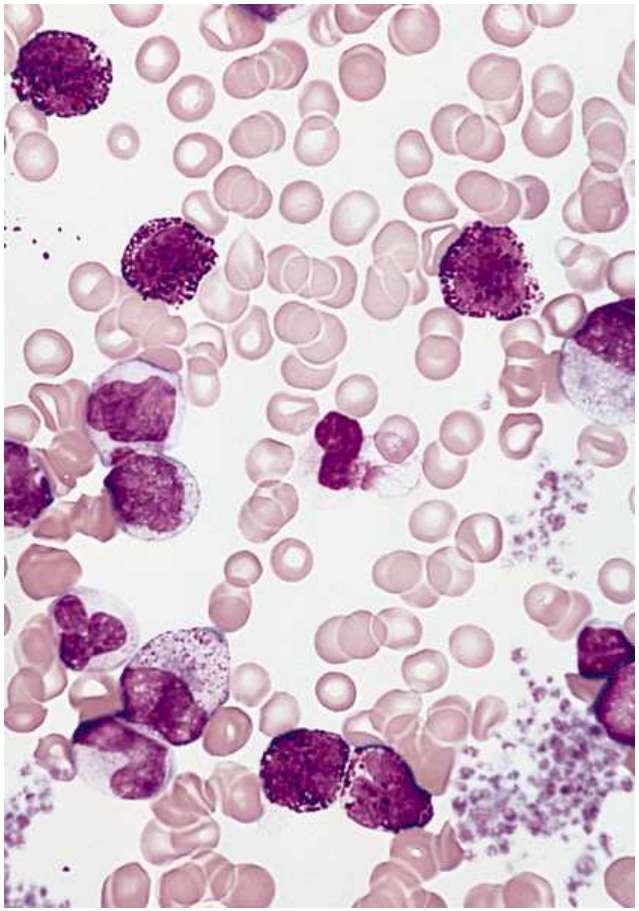
Chronic myeloid leukemia

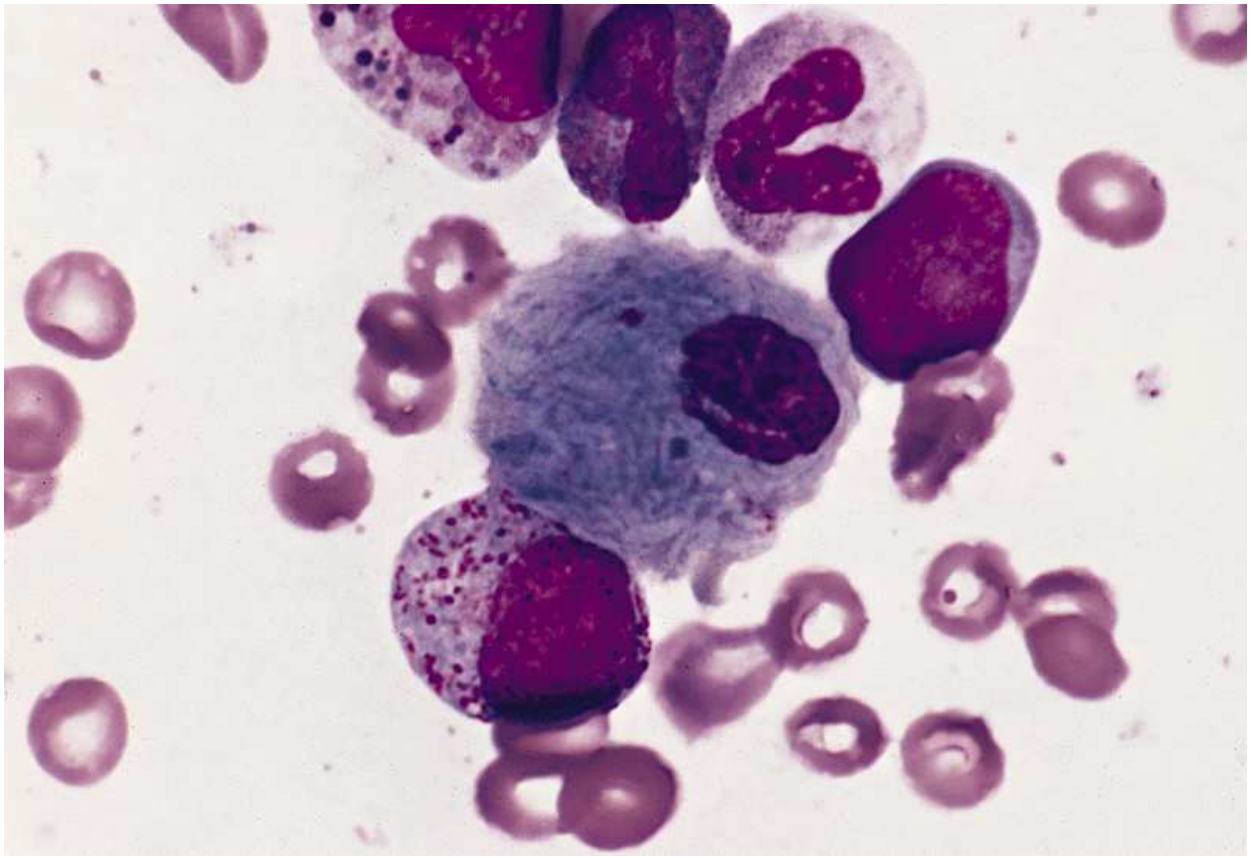


Three basophils and all stages of neutrophil maturation, including two early promyelocytes, are shown. The increased platelets are normal in appearance. (Wright-Giemsa stain)

Fig. 225

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Chronic myeloid leukemia

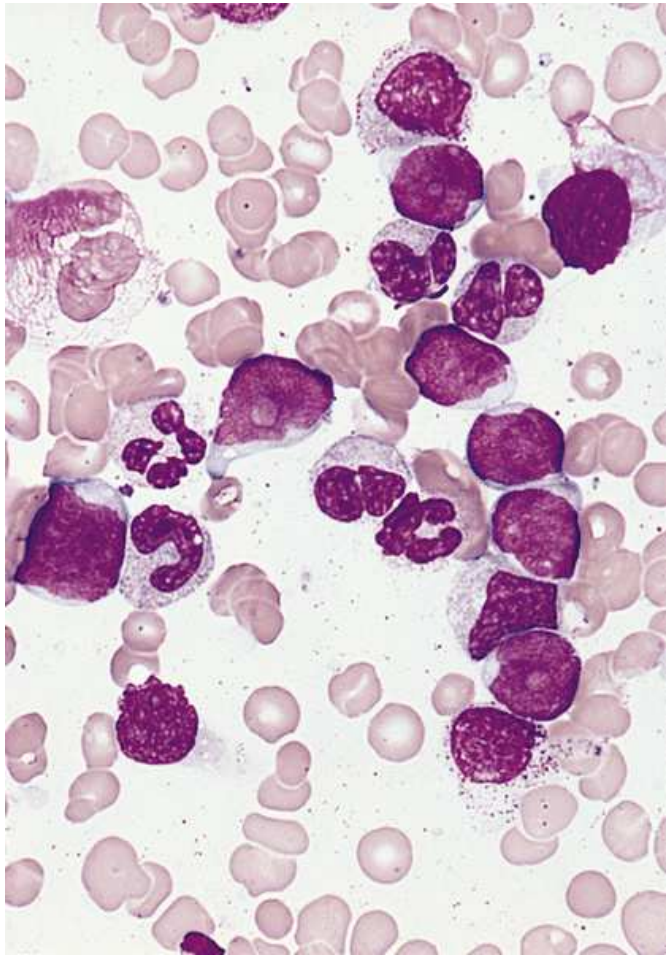


Pseudo-Gaucher cell.

Fig. 2257

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Chronic myeloid leukemia



Bone marrow smear from a patient with CML in myeloblastic transformation. Approximately 50 percent of the leukocytes are blasts. (Wright-Giemsa stain).

Fig. 235

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Chronic myeloid leukemia

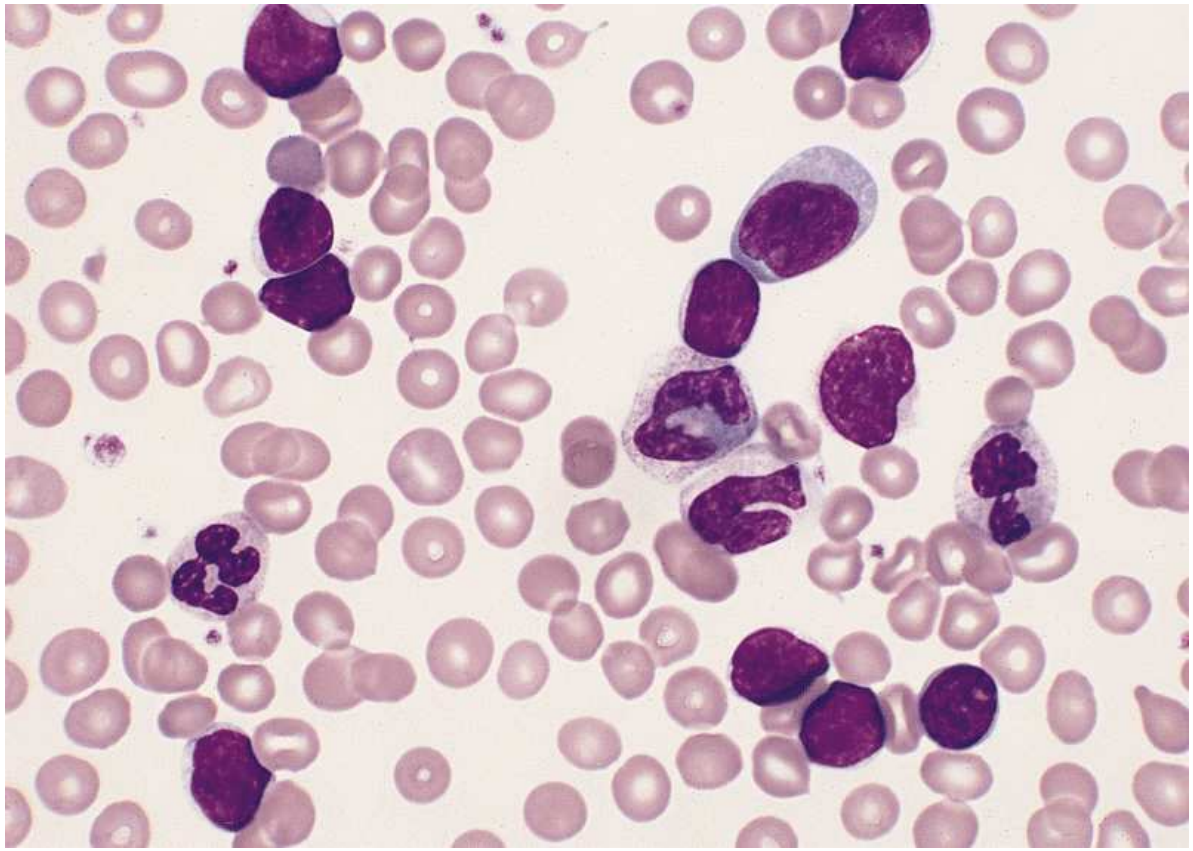


Fig. 250

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Blood smear from a 56-year-old woman with a Ph1 positive chronic myelogenous leukemia, presenting with a leukocyte count of 200,000/fL. Forty-one percent of the white cells are lymphoblasts (small with a high nuclear-cytoplasmic ratio, condensed nuclear chromatin, and generally indistinct or no evident nucleoli). TdT positive. (Wright-Giemsa stain)..

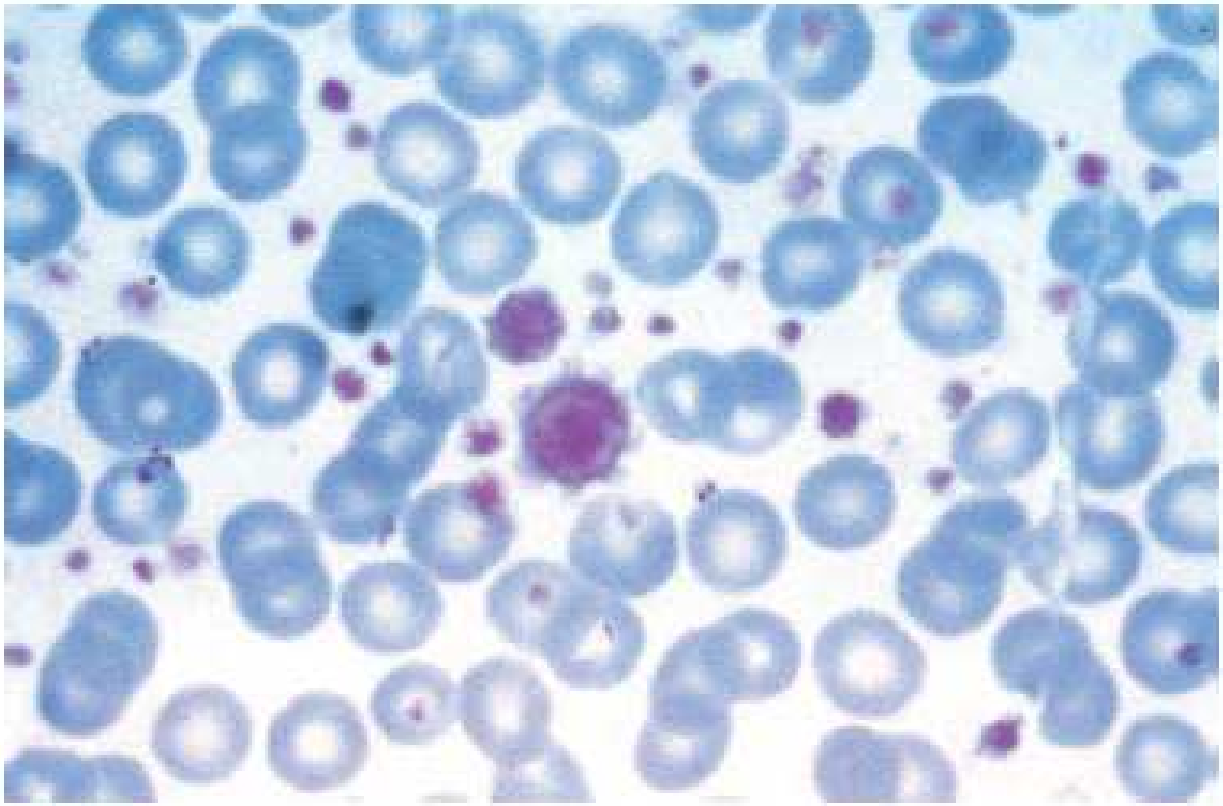


Figure 13-36 Essential thrombocytosis. Peripheral blood smear shows marked thrombocytosis, including giant platelets approximating the size of surrounding red cells.

Atypical chronic myelocytic leukemia

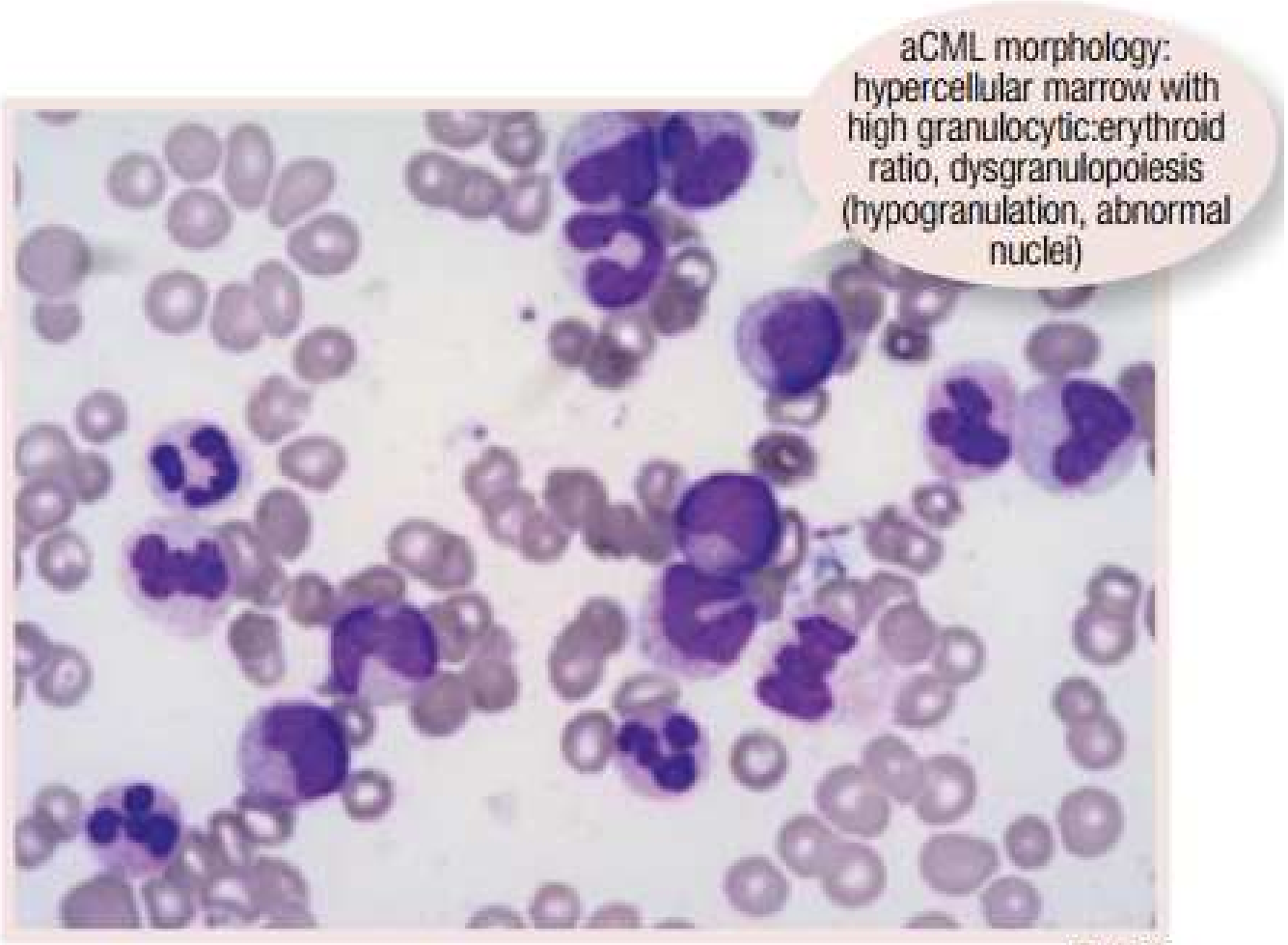
- aCML is a rare disease of the elderly with a dismal prognosis (median survival ~24 months) and frequent (40%) transformation to AML.
- Diagnostic criteria include hyperleukocytosis with >10% neutrophil precursors, dysgranulopoiesis, no or minimal basophilia and monocytosis, hypercellular BM with granulocytic proliferation and dysplasia. Classical MPN, including BCR-ABL CML and AML, must all be excluded.

Atypical chronic myelocytic leukemia

- SETBP1 and ETKN1 mutations are found in up to one third of cases.
- CSF3R mutations are rare and warrant exclusion of chronic neutrophilic leukemia.

Chronic myelomonocytic leukemia

- Absolute peripheral monocytosis with/without dysgranulopoiesis
- Splenomegaly in 32%
- 17-53% leukemic conversion
- 18 month median survival
- hydroxyurea palliation
- Consider in cases of Ph negative CML



aCML, Atypical chronic myeloid leukaemia.

Fig. 15.9

Chronic myeloproliferative disorders

- Primary Myelofibrosis is characterized by fibrosis in bone marrow and splenomegaly.
- Leukoerythroblastosis and tear drop cells
- Philadelphia chromosome negative.
- Del 13q, del 15q, del 20q, del 7, trisomy 8, trisomy 9, i17, inv 3, 12p-, 11q23 rearrangements associated with poor prognosis
- IL6, TIMP1, MIP1b, IGFBP2, TGFβ, and PDGF overproduction.
- AKT/mTOR may also be activated.

CML risk factors

- Hemoglobin <10.0 g/dL
- The need for red cell transfusions
- Platelet count <100,000ul
- Unfavorable karyotype
- Age >65years
- WBC >25,000/fl
- Circulating blasts >1%

CML risk factors

- If no risk factors at diagnosis, median survival is 15.4 years
- If one risk factor, 6.5 years
- 2 or 3 risk factors, 2.9 years
- If 4 risk factors, 1.3 years.
- 10% transformation rate to myelogenous leukemia.
- If only 1 risk factor and JAK mutation, the JAK1/2 inhibitor, ruxolitinib is employed as therapy.
- If 2-3 risk factors, and less than 65 years of age, proceed to allogenic marrow transplant.
- If 5q- karyotype and symptomatic, lenalidomide is employed as therapy.

Polycythemia vera

- Polycythemia vera (increased red cell mass) and essential thrombocythemia often show similar traits of markedly elevated thrombocyte counts or elevated levels of hemoglobin and have a tendency to secondary bone marrow fibrosis.
- Clonal stem cell disorders.
- JAK2 mutation in all polycythemia vera cases.
- 10 year median survival. 1
- 1-5% yearly transformation rate to acute leukemia.
- May see massive splenomegaly
- May lead to (secondary) myelofibrosis.

Table 14-8 Pathophysiologic Classification of Polycythemia

Relative
Reduced plasma volume (hemoconcentration)
Absolute
Primary (Low Erythropoietin)
Polycythemia vera
Inherited erythropoietin receptor mutations (rare)
Secondary (High Erythropoietin)
Compensatory
Lung disease
High-altitude living
Cyanotic heart disease
Paraneoplastic
Erythropoietin-secreting tumors (e.g., renal cell carcinoma, hepatocellular carcinoma, cerebellar hemangioblastoma)
Hemoglobin mutants with high O_2 affinity
Inherited defects that stabilize HIF-1α
Chuvash polycythemia (homozygous *VHL* mutations)
Prolyl hydroxylase mutations

HIF-1α, Hypoxia-induced factor 1α.

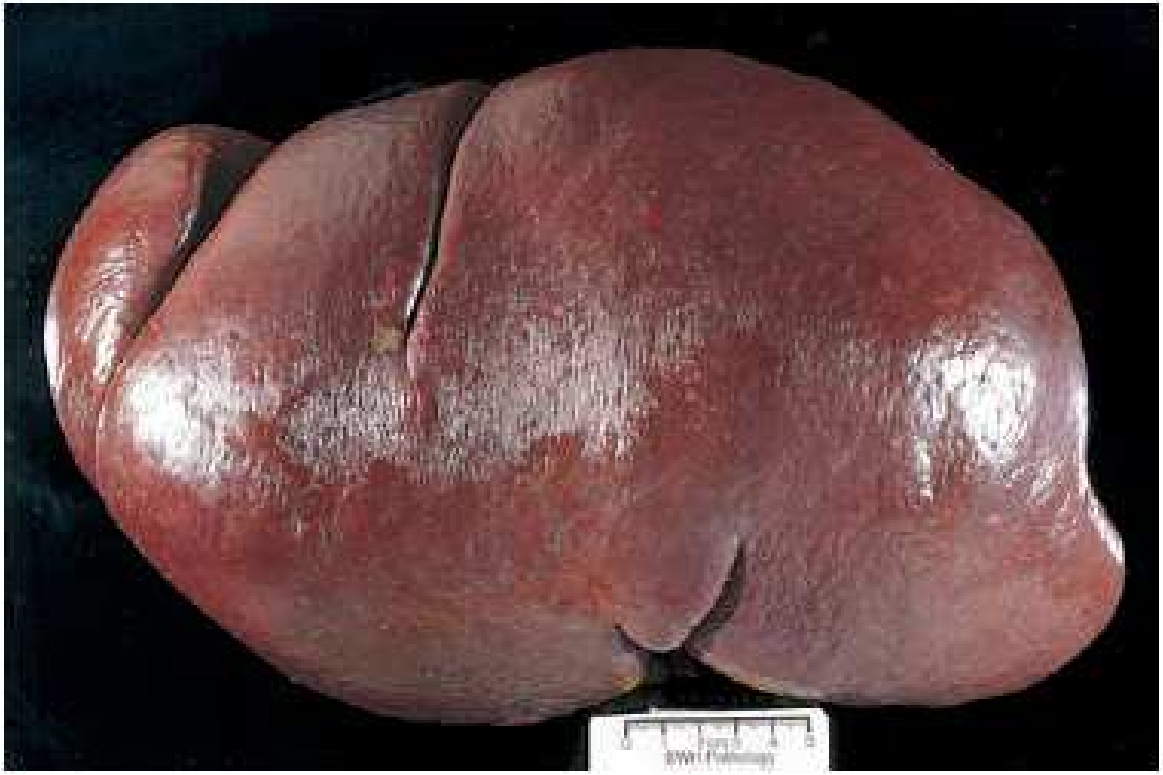


Figure 13-35 Polycythemia vera, spent phase. Massive splenomegaly (3020 gm; normal: 150 to 200 gm) largely due to extramedullary hematopoiesis occurring in the setting of advanced marrow myelofibrosis. (Courtesy Dr. Mark Fleming, Department of Pathology, Children's Hospital, Boston, Mass.)

Essential thrombocythemia

- Largely found in females.
- Median age 60 years
- May seen in those younger than 40.
- 50% JAK2 mutations
- 10% MPL mutations
- Tyrosine kinase activated by thrombopoietin
- Platelet count >450,000/fl, megakaryocytic hyperplasia on bone marrow biopsy, absence of the Philadelphia chromosome (BCR-ABL gene rearrangement), and normal iron stores are necessary for a diagnosis of essential thrombocythemia.
- 20+ year survival if young, no previous thrombosis.

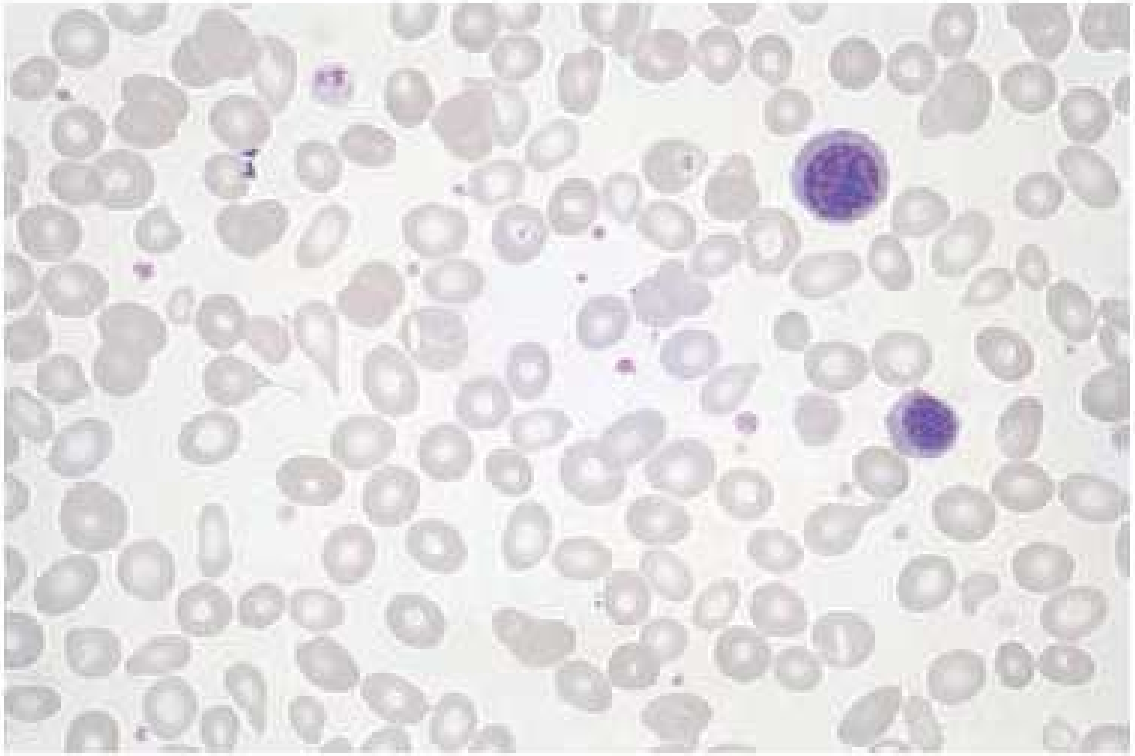


Figure 13-37 Primary myelofibrosis (peripheral blood smear). Two nucleated erythroid precursors and several teardrop-shaped red cells (dacryocytes) are evident. Immature myeloid cells were present in other fields. An identical picture can be seen in other diseases producing marrow distortion and fibrosis.

Table 2. Mastocytosis types and subtypes.

Cutaneous mastocytosis
Urticaria pigmentosa/Maculopapular cutaneous mastocytosis
Monomorphic
Polymorphic
Diffuse cutaneous mastocytosis
Cutaneous mastocytoma
Isolated mastocytoma
Multilocalized mastocytoma
Systemic mastocytosis
Bone marrow mastocytosis
Indolent systemic mastocytosis
Smoldering systemic mastocytosis
Aggressive systemic mastocytosis
Systemic mastocytosis with an associated haematologic neoplasm
Mast cell leukemia
Mast cell sarcoma

Note: Well-differentiated systemic mastocytosis (WDSM) represents a morphologic variant that may occur in any SM type/subtype, including mast cell leukaemia.

2016 WHO CLASSIFICATION OF MDS[a,b,1]

Subtype	Blood	Bone Marrow
MDS with single lineage dysplasia (MDS-SLD)[c]	Single or bicytopenia	Dysplasia in ≥10% of one cell line, <5% blasts[d,2]
MDS with ring sideroblasts (MDS-RS)	Anemia, no blasts	≥15% of erythroid precursors w/ring sideroblasts, or ≥5% ring sideroblasts if *SF3B1* mutation present
MDS with multilineage dysplasia (MDS-MLD)	Cytopenia(s), <1 x 10^9/L monocytes	Dysplasia in ≥10% of cells in ≥2 hematopoietic lineages, <15% ring sideroblasts (or <5% ring sideroblasts if *SF3B1* mutation present), <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2%–4% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 5%–9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5%–19% blasts, <1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, 10%–19% blasts, ± Auer rods
MDS, unclassifiable (MDS-U)	Cytopenias, ±1% blasts on at least 2 occasions	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, <5% blasts
MDS with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts ± one other abnormality except -7/del(7q)
Refractory cytopenia of childhood (Provisional WHO category)	Cytopenias, <2% blasts	Dysplasia in 1–3 lineages, <5% blasts

MYELODYSPLASTIC/MYELOPROLIFERATIVE OVERLAP NEOPLASMS (MDS/MPN), 2017 WHO CLASSIFICATION AND MANAGEMENT[1,2]

Subtype	Blood	Bone Marrow	Frequent Mutations	Treatment
Chronic myelomonocytic leukemia (CMML)-0	>1x10^9/L monocytes, <2% blasts ≥10% monocytes	Dysplasia in ≥1 hematopoietic line, <5% blasts	*TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL*[3,4]	Observation[e,f,11-21]
CMML-1	>1x10^9/L monocytes, 2%–4% blasts ≥10% monocytes	Dysplasia in ≥1 hematopoietic line, 5%–9% blasts	*TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL*[3,4]	Consider HMA[e,f, 11-21]
CMML-2	>1x10^9/L monocytes, 5%–19% blasts or Auer rods ≥10% monocytes	Dysplasia in ≥1 hematopoietic line, 10%–19% blasts or Auer rods	*TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL*[3,4]	HMA ± ruxolitinib and/or allogeneic HSCT[e,f,11-24]
Atypical chronic myeloid leukemia (aCML), *BCR-ABL* negative[g]	WBC >13x10^9/L, neutrophil precursors ≥10%, <20% blasts, dysgranulopoiesis	Hypercellular, <20% blasts	*SETBP1, ETNK1*[5]	Consider HMA and/or ruxolitinib and/or allogeneic HSCT[h,25,26]
Juvenile myelomonocytic leukemia (JMML)	>1x10^9/L monocytes, <20% blasts ≥10% monocytes, increased HbF	>1x10^9/L monocytes <20% blasts Ph negative GM-CSF hypersensitive	*PTPN11, NF1, N/KRAS, CBL, SETBP1, JAK3*[6,7]	Allogeneic HSCT
MDS/MPN, unclassifiable ("Overlap syndrome")	Dysplasia + myeloproliferative features, No prior MDS or MPN	Dysplasia + myeloproliferative features	*TET2, NRAS, RUNX1, CBL, SETBP1, ASXL1*[8]	Consider HMA and/ or allogeneic HSCT
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/ MPN-RS-T)	Dysplasia + myeloproliferative features, platelets ≥450 x10^9/L, ≥15% ring sideroblasts	Dysplasia + myeloproliferative features	*SF3B1, JAK2*[9,10] *MPL, CALR*	Consider HMA and/ or lenalidomide[27]

INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)[a,1]

Survival and AML Evolution					
	Score Value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)[b]	<5	5-10	—	11-20	21-30
Karyotype[c]	Good	Intermediate	Poor	—	—
Cytopenia[d]	0/1	2/3	—	—	—

IPSS Risk Category (% IPSS pop.)	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥2.5	0.4	0.2

For IPSS: Low/Intermediate-1, see MDS-3 and MDS-4
For IPSS: Intermediate-2/High, see MDS-6

[a]IPSS should be used for initial prognostic and planning purposes. WPSS permits dynamic estimation of prognosis at multiple time points during the course of MDS.
[b]Patients with 20%–29% blasts may be considered to have MDS (FAB) or AML (WHO).

REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R[2])

	Score Value						
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetic[e]	Very good	—	Good	—	Intermediate	Poor	Very Poor
Marrow blasts (%)	≤2	—	>2-<5	—	5-10	>10	—
Hemoglobin	≥10	—	8-<10	<8	—	—	—
Platelets	≥100	50-<100	<50	—	—	—	—
ANC	≥0.8	<0.8	—	—	—	—	—

IPSS-R Risk Category (% IPSS-R pop.)	Overall Score	Median Survival (y) in the Absence of Therapy	25% AML Progression (y) in the Absence of Therapy
VERY LOW (19)	≤1.5	8.8	Not reached
LOW (38)	>1.5-≤3.0	5.3	10.8
INT[3] (20)	>3.0-≤4.5	3	3.2
HIGH (13)	>4.5-≤6.0	1.6	1.4
VERY HIGH (10)	>6.0	0.8	0.7

For IPSS-R: Very Low/Low/Intermediate, see MDS-3 and MDS-4
For IPSS-R: Intermediate/High/Very High, see MDS-6

WHO-BASED PROGNOSTIC SCORING SYSTEM (WPSS)[3,4]

Variable	Variable Scores			
	0	1	2	3
WHO category	RCUD, RARS, MDS with isolated del(5q)	RCMD	RAEB-1	RAEB-2
Karyotype[f]	Good	Intermediate	Poor	—
Severe anemia (hemoglobin <9 g/dL in males or <8 g/dL in females)	Absent	Present	—	—

WPSS Risk	Sum of Individual Variable Scores	Median Survival (y) from Diagnosis	Median Time (y) to AML Progression from Diagnosis
Very Low	0	11.6	NR
Low	1	9.3	14.7
Intermediate	2	5.7	7.8
High	3–4	1.8	1.8
Very High	5–6	1.1	1.0

Mutated Gene[b]	Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes[c]	Overall Incidence	Clinical Significance
TET2	Nonsense or Frameshift or Splice Site Missense: any in codons 1134–1444 or 1842–1921	20%–25%	Associated with normal karyotypes. More frequent in CMML (40%–60%). Common in clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS).
DNMT3A	Nonsense or Frameshift or Splice Site Missense in codons G543, R635, S741, R736, R739, S770, M880, R882, W893, P904, A910	12%–18%	More frequent occurrence in AML, particularly R882 mutations. Common in CHIP and CCUS.
ASXL1	Nonsense or Frameshift	15%–25%	Independently associated with a poor prognosis in MDS and CMML. More frequent in CMML (40%–50%). Common in CHIP and CCUS.
EZH2	Nonsense or Frameshift	5%–10%	Independently associated with a poor prognosis in MDS and MDS/MPN. More frequent in CMML (12%).
SF3B1	Missense: E622, Y623, R625, N626, H662, T663, K666, K700E, I704, G740, G742, D781	20%–30%	Strongly associated with ring sideroblasts and more frequent in MDS-RS (80%). Independently associated with a more favorable prognosis.
SRSF2	Missense or In-Frame Deletion: involving codon P95	10%–15%	More frequent in CMML (40%) and associated with a poor prognosis.
U2AF1	Missense: S34, Q157	8%–12%	Associated with a poor prognosis.
ZRSR2	Nonsense or Frameshift	5%–10%	Associated with a poor prognosis.
RUNX1[d]	Nonsense or Frameshift	10%–15%	Independently associated with a poor prognosis in MDS.
TP53[d]	Nonsense or Frameshift or Splice Site Missense: any in codons except P47S and P72R	8%–12%	Independently associated with a poor prognosis. More frequent with complex karyotypes (50%) and del(5q) (15%–20%). May predict resistance or relapse to lenalidomide.
STAG2	Nonsense or Frameshift or Splice Site	5%–10%	Associated with a poor prognosis.
NRAS[d]	Missense: G12, G13, Q61	5%–10%	Associated with a poor prognosis, particularly in patients predicted to have lower-risk MDS. More frequent in CMML and JMML (~15%).
CBL[d]	Missense: any in codons 366–420	<5%	More frequent in CMML (10%–20%) and JMML (15%).
NF1[d]	Nonsense or Frameshift or Splice Site	<5%	More frequent in CMML (5%–10%) and in JMML (30%) where it is often germline.

Mutated Gene[b]	Examples of Typical Somatic Mutation Types and Locations in Select MDS-Related Genes[c]	Overall Incidence	Clinical Significance
JAK2	Missense: V617F	<5%	More frequent in MDS/MPN-RS-T (50%); can occur in conjunction with *SF3B1*.
CALR	Frameshift: after codon 352	<5%	Observed in MDS/MPN-RS&T where it can occur in conjunction with *SF3B1* mutations.
MPL	Missense: W515L/K	<5%	Observed in MDS/MPN-RS&T where it can occur in conjunction with *SF3B1* mutations.
ETV6[d]	Nonsense or Frameshift	<5%	Independently associated with a poor prognosis.
GATA2[d]	Nonsense or Frameshift or Splice Site Missense: in codons 349–398		Associated with a poor prognosis.
DDX41[d]	Nonsense or Frameshift or Splice Site Missense: in codon R525H		Constitutional (germline) mutations in this gene can occur.
IDH1	Missense: R132	<5%	More frequent in AML.
IDH2	Missense: R140Q, R172	<5%	More frequent in AML. Associated with a poor prognosis.
SETBP1	Missense: E858, T864, I865, D868, S869, G870	<5%	Associated with disease progression. More frequent in CMML (5%–10%) and JMML (7%).
PHF6	Nonsense or Frameshift or Splice Site	<5%	More frequent in cases with excess blasts, but no association with survival.
BCOR	Nonsense or Frameshift or Splice Site	<5%	Associated with a poor prognosis. More frequent in CMML (5%–10%).
FLT3	Internal Tandem Duplication or Missense: in codon D835		Associated with a poor prognosis.
WT1	Nonsense or Frameshift or Splice Site		Associated with a poor prognosis.
NPM1	Frameshift: W288fs*12		Associated with a poor prognosis.
STAT3	Missense: any codons 584–674	<5%	Occurs in large granular lymphocyte leukemia (LGL) associated with MDS; associated with immune bone marrow failure.
PPM1D	Nonsense or Frameshift	~5%	Associated with therapy-related MDS, but not associated with adverse prognosis independent of *TP53*. Common in CHIP and CCUS.

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

Germline predisposition for myeloid neoplasms *without* cytopenia(s), dysplasia, or other organ dysfunction prior to myeloid malignancy presentation			
Disorder	**Gene**	**Hematologic Findings/ Myeloid Malignancy**	**Other Phenotypes and Clinical Features**
CEBPA[1]	*CEBPA*	AML	AML is often favorable risk, somatic *CEBPA* mutations are a frequent second event (with different somatic mutations occurring with AML recurrence[2]), ~ 5%–10% of *CEBPA* double-mutant AML cases harbor germline mutations.[3]
DDX41[4]	*DDX41*	AML, MDS, CML	Late age of onset of hematologic malignancies; NHL, Hodgkin lymphoma.[5]
14q32.2 genomic duplication[6]	Includes *ATG2B* and *GSKIP*	AML, MPN, CMML (highly penetrant)	Familial MPN. Earlier age of onset compared to sporadic MPN.

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

Germline predisposition for myeloid neoplasms *with* pre-existing cytopenia(s) and/or other organ dysfunction prior to myeloid malignancy presentation			
Disorder	**Gene**	**Hematologic Findings/ Myeloid Malignancy**	**Other Phenotypes and Clinical Features**
ANKRD26[7]	*ANKRD26*	Moderate thrombocytopenia with mild bleeding manifestations; platelet size is usually not enlarged; dysmegakaryopoiesis[8]/AML, MDS	
ETV6[9,10]	*ETV6*	Thrombocytopenia and mild bleeding manifestations; platelet size is usually not enlarged[11]/AML, MDS	ALL (typically precursor B-cell ALL)[9,11]
GATA2 deficiency syndrome[12,13]	*GATA2*	Bone marrow failure; B-/NK-/CD4-cell lymphocytopenia, monocytopenia[14]/AML/ MDS (highly penetrant)	Immune deficiency (viral infections, warts, disseminated nontuberculous mycobacterial infections), wide range of extra-hematopoietic manifestations (eg, lymphedema, sensorineural hearing loss, pulmonary alveolar proteinosis[15]).
Familial platelet disorder with associated myeloid malignancy[b,16,17]	*RUNX1*	Thrombocytopenia and abnormal platelet function/AML/MDS (highly penetrant)	Typical age of onset of AML/MDS is 20–40 y. Anticipation may lead to occurrence in younger individuals in subsequent generations; eczema; ALL.
MIRAGE syndrome[18]	*SAMD9*	Transient or permanent cytopenias and marrow failure/AML, MDS	Typically presents in infancy; phenotype associated with inherited mutations as opposed to de novo mutations may be less severe[19]; myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; MDS with monosomy 7/-7q, somatic genetic aberrations in hematopoietic cells often occur that result in loss of the mutant *SAMD9* allele.[18]
Ataxia-pancytopenia syndrome[20,21]	*SAMD9L*	Transient or permanent cytopenias and marrow failure/AML, MDS	Variable neurologic findings (eg, gait disturbance, nystagmus, cerebellar atrophy and white matter hyperintensities[22]); immune deficiency; MDS with monosomy 7/-7q, somatic genetic aberrations in hematopoietic cells often occur that result in loss of the mutant *SAMD9* allele.[20]
SRP72[23]	*SRP72*	Marrow failure/MDS	Congenital sensorineural deafness.

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

Classical inherited bone marrow failure syndromes			
Disorder	**Gene**	**Hematologic Findings/ Myeloid Malignancy**	**Other Phenotypes and Clinical Features**
Diamond-Blackfan anemia[c]	*RPL5, RPL11, RPL15, RPL23, RPL26, RPL27, RPL31, RPL35A, RPS7, RPS10, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29, TSR2, GATA1*	Anemia and marrow erythroid hypoplasia/ AML, MDS	Cardiac anomalies, Cathie facies, genitourinary anomalies, cleft lip/palate, short stature; sarcomas; elevated erythrocyte adenosine deaminase.
Fanconi anemia[d,e]	*FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCDE, FANCF, FANCG, FANCI, FANCJ/BRIP1/BACH1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANQ/ERCC4, FANCR/ RAD51, FANCS/BRCA1, FANCT/UNE2T, FANCU/XRCC2, FANCV/REV7*	Bone marrow failure/AML, MDS	Short stature, skin pigmentation (café-au-lait or hypopigmented spots), skeletal anomalies (thumbs, arms), multiple other congenital anomalies; squamous cell carcinomas of head/neck/vulva/vagina, liver tumors, additional solid tumors associated with *FANCD1* include brain and Wilms tumors; therapy-related neoplasms may emerge after treatment for solid tumors; increased chromosome fragility.
Shwachman-Diamond syndrome[f]	*SBDS, EFL1, DNAJC21*	Bone marrow failure/AML, MDS	Pancreatic insufficiency, skeletal abnormalities; low serum trypsinogen or pancreatic isoamylase.
Telomere biology disorders[g]	*ACD, CTC1, DKC1, NAF1, NHP2, NOP10, PARN, POT1, RTEL1, TERC, TERT, TINF2, USB1, WRAP53*	Bone marrow failure/AML, MDS	Idiopathic pulmonary fibrosis, emphysema, early hair graying, osteoporosis, pulmonary arteriovenous malformations and hepatopulmonary syndrome, liver fibrosis-cirrhosis, esophageal stricture, enterocolitis, immune deficiency; rare cases manifest as dyskeratosis congenita with nail dystrophy, rash, oral leukoplakia; squamous cell carcinomas of head/neck/GI tract; shortened telomere lengths.
Congenital neutropenia	*ELANE, G6PC3, GFI1, HAX1*	Neutropenia/AML, MDS	
Myeloid neoplasms associated with Down syndrome	*Trisomy 21, GATA1*	Transient abnormal myelopoiesis/AML, MDS	Down syndrome; acute megakaryoblastic leukemia.

GENE MUTATIONS ASSOCIATED WITH HEREDITARY MYELOID MALIGNANCIES[a]

Germline predispositions for myeloid neoplasms and solid tumor cancers			
Disorder	**Gene**	**Hematologic Findings/ Myeloid Malignancy**	**Other Phenotypes and Clinical Features**
Constitutional mismatch repair deficiency	*EPCAM, MLH1, MSH2, MSH6, PMS2*	AML, MDS	Café-au-lait spots; ALL, lymphomas, central nervous system, GI, and other tumors; microsatellite instability of tumor cells.
Hereditary breast and ovarian cancer[d]	*BRCA1, BRCA2*	AML, MDS	Breast and ovarian cancers, other tumors. Therapy-related neoplasms may emerge after treatment for solid tumors.
Li-Fraumeni syndrome	*TP53*	AML, MDS	AML and MDS are associated with complex karyotypes as seen with somatic *TP53* mutations; ALL, adrenocortical carcinoma, brain cancer, breast cancer, choroid plexus carcinoma, colon cancer, lung carcinoma, sarcoma, other tumors; therapy-related neoplasms may emerge after treatment for solid tumors.
RASopathies	*CBL, KRAS, NF1, PTPN11*	AML, MDS	Mutations induce constitutive activation of RAS/MAPK pathways and cause many syndromic findings and hematologic and solid tumor cancer risk (neuro-cardio-fascio cutaneous syndrome), eg, neurofibromatosis type 1 and Noonan syndrome, which predispose to development of JMML or an MPN.
Other rare DNA repair syndromes	*BLM, MBD4*	AML, *MBD4:* early-onset AML with a high somatic mutation burden characterized by CG>TG changes including biallelic CG>TG mutations in DNMT3A[24]	Bloom syndrome: pre- and postnatal growth retardation, photosensitive skin changes, immunodeficiency, insulin resistance, microcephaly, high-pitched voice, hypogonadism, and increased risk of early onset of multiple cancers.

SPECTRUM OF INDOLENT MYELOID HEMATOPOIETIC DISORDERS[a,b,c,d,e]

Feature	ICUS	IDUS	CHIP	CCUS	MDS
Somatic mutation	–	–	+/–[c]	+/–[c]	+/–
Clonal karyotypic abnomality	–	–	+/–[c]	+/–[c]	+/–
Marrow dysplasia	–	+	–	–	+
Cytopenia	+	–	–	+	+

ICUS: Idiopathic cytopenia of unknown significance
IDUS: Idiopathic dysplasia of unknown significance
CHIP: Clonal hematopoiesis of indeterminate potential
CCUS: Clonal cytopenia of unknown significance
MDS: Myelodysplastic syndromes

EVIDENCE BLOCKS FOR INITIAL TREATMENT OF LOW/INTERMEDIATE-1 RISK MDS WITH CLINICALLY RELEVANT THROMBOCYTOPENIA OR NEUTROPENIA OR INCREASED MARROW BLASTS

Azacitidine	
Decitabine	
Equine ATG (for select patients)	
Equine ATG + cyclosporin (for select patients)	

EVIDENCE BLOCKS FOR INITIAL TREATMENT OF SYMPTOMATIC ANEMIA

Initial treatment for symptomatic anemia with del(5q) ± one other cytogenetic abnormality (except those involving chromosome 7) (MDS-4)

Darbepoetin (for select patients)	
Darbepoetin + G-CSF (for select patients)	
Epoetin alfa (for select patients)	
Epoetin alfa + G-CSF (for select patients)	
Lenalidomide	

Initial treatment for symptomatic anemia, no del(5q) ± other cytogenetic abnormalities, serum EPO ≤500 mU/mL; for ring sideroblasts <15% or ring sideroblasts <5% without an *SF3B1* mutation (MDS-4), (MDS-5)

Darbepoetin	
Darbepoetin + G-CSF (if no response to darbepoetin alone)	
Darbepoetin + lenalidomide (if no response to darbepoetin alone)	
Epoetin alfa	
Epoetin alfa + G-CSF (if no response to epoetin alfa alone)	
Epoetin alfa + lenalidomide (if no response to epoetin alfa alone)	

Initial treatment for symptomatic anemia, no del(5q) ± other cytogenetic abnormalities, serum EPO ≤500 mU/mL; for ring sideroblasts ≥15% or ring sideroblasts ≥5% with an *SF3B1* mutation (MDS-4), (MDS-5)

Darbepoetin + G-CSF	
Epoetin alfa + G-CSF	
Luspatercept-aamt (if no response to darbepoetin + G-CSF or epoetin alfa + G-CSF)	

Initial treatment for symptomatic anemia, no del(5q) ± other cytogenetic abnormalities, serum EPO >500 mU/mL; for ring sideroblasts <15% or ring sideroblasts <5% without an *SF3B1* mutation (MDS-4), (MDS-5)

Equine ATG (if good probability to respond to IST)	
Equine ATG + cyclosporin (if good probability to respond to IST)	
Azacitidine (if no response to equine ATG ± cyclosporin or poor probability to response to IST)	
Decitabine (if no response to equine ATG ± cyclosporin or poor probability to response to IST)	
Lenalidomide (if no response to equine ATG ± cyclosporin or poor probability to respond to IST)	

Initial treatment for symptomatic anemia, no del(5q) ± other cytogenetic abnormalities, serum EPO >500 mU/mL; for ring sideroblasts ≥15% or ring sideroblasts ≥5% with an *SF3B1* mutation (MDS-5)

Luspatercept-aamt	

EVIDENCE BLOCKS FOR SUBSEQUENT TREATMENT OF SYMPTOMATIC ANEMIA

Subsequent line therapy for symptomatic anemia with del(5q) ± one other cytogenetic abnormality (except those involving chromosome 7); for patients who did not respond to lenalidomide (MDS-4), (MDS-5)

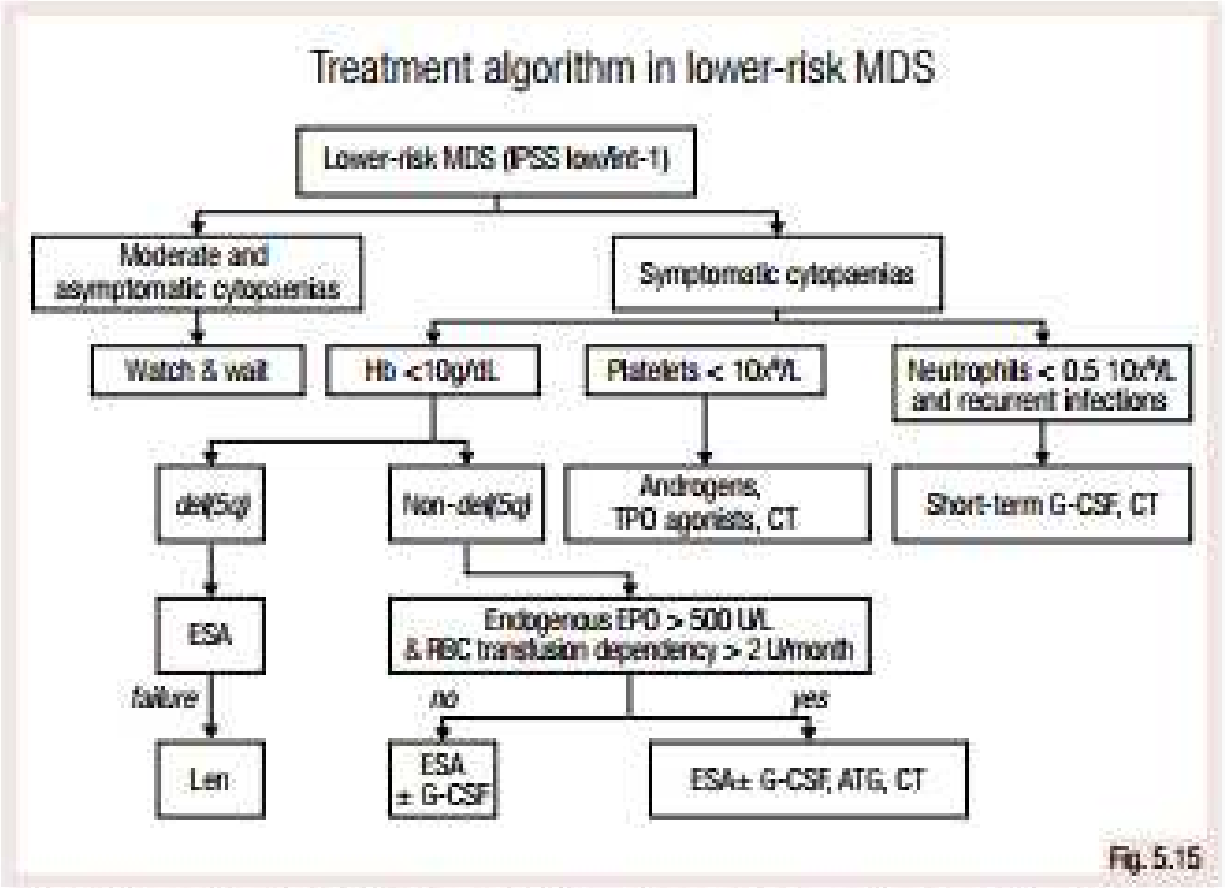
Azacitidine (if poor probability to respond to IST or no response to IST)	
Decitabine (if poor probability to respond to IST or no response to IST)	
Lenalidomide (if poor probability to respond to IST or no response to IST)	

Subsequent line therapy for symptomatic anemia, no del(5q) ± other cytogenetic abnormalities, serum EPO ≤500 mU/mL; for ring sideroblasts <15% or ring sideroblasts <5% without an *SF3B1* mutation; for patients who did not respond to ESAs + lenalidomide or ESAs + G-CSF (MDS-4), (MDS-5)

Azacitidine (if no response to ESAs/IST or poor probability to respond to IST)	
Decitabine (if no response to ESAs/IST or poor probability to respond to IST)	
Lenalidomide (if no response to ESAs/IST or poor probability to respond to IST)	

Subsequent line therapy for symptomatic anemia, no del(5q) ± other cytogenetic abnormalities, serum EPO ≤500 mU/mL; for ring sideroblasts ≥15% or ring sideroblasts ≥5% with an *SF3B1* mutation; for patients who did not respond to luspatercept-aamt (MDS-4), (MDS-5)

Equine ATG (if good probability to respond to IST)	
Equine ATG + cyclosporin (if good probability to respond to IST)	
Azacitidine (if poor probability to respond to IST or no response to IST)	
Decitabine (if poor probability to respond to IST or no response to IST)	
Lenalidomide (if poor probability to respond to IST or no response to IST)	



ATG, Anti-thymocyte globulin; CT, clinical trial; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, haemoglobin; IPSS, International Prognostic Scoring System; Len, lenalidomide; MDS, myelodysplastic syndromes; RBC, red blood cell; TPO, thrombopoietin.

Treatment

- Allogenic stem cell transplant should be considered in all patients with higher- risk MDS (IPSS intermediate-2/high, IPSS-R high/very high) or otherwise delayed, except perhaps in some IPSS-R intermediate patients.
- Hypomethylating agents are active in higher-risk MDS.
- 16% may benefit from low dose cytarabine
- Short lived improvement with13-cis-retinoic acid in small subset of patients (20%), pyridoxine (1%)
- Azacytidine improves overall survival over conventional care in patients not eligible for transplant.

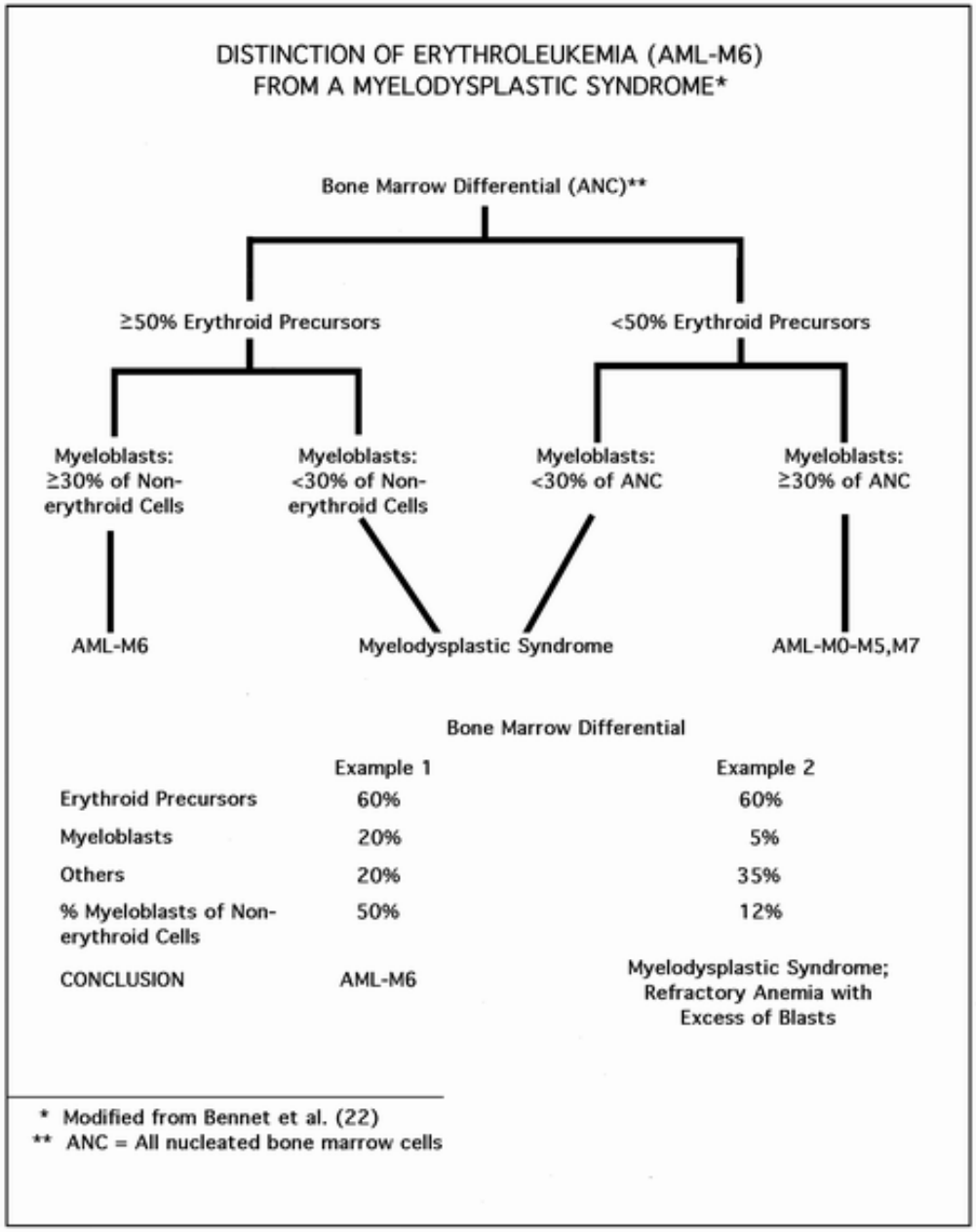


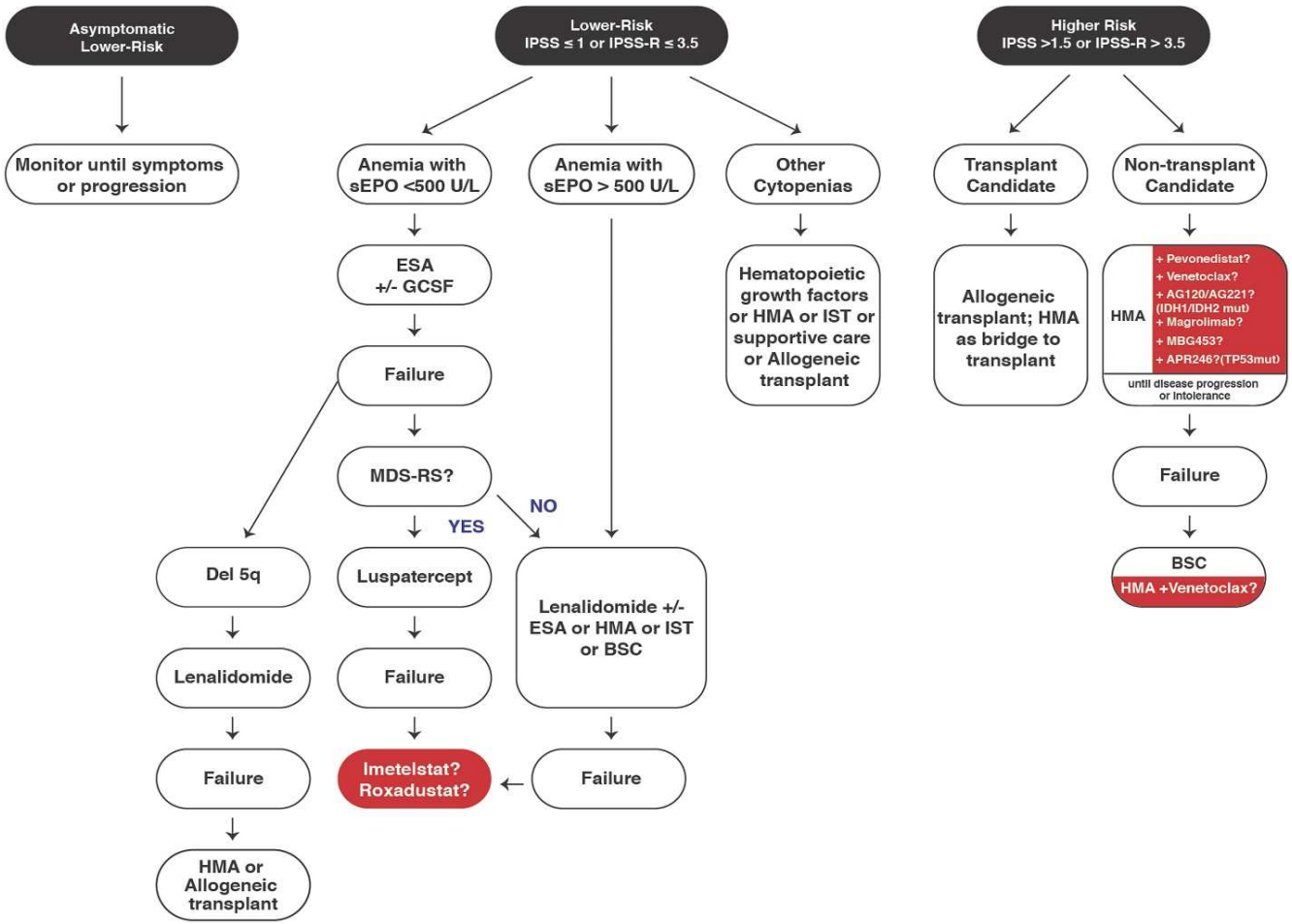
Fig. 80

McKenna, Robert W, and Brunning, Richard D, “Tumors of the bone marrow.” Atlas of Tumor Pathology. Third series. Fascicle 9. Armed Forces Institute of Pathology. Washington, DC. 1994.

Modified from Bennett JM, Catovsky D, Daniel MT, et al. Proposed revised criteria for the classification of acute myeloid leukemia. A report of the French-American-British Cooperative Group. Ann Intern Med 1985;103:626-9.

Current (and potentially future) Treatment Algorithm in Myelodysplastic Syndromes

Consider clinical trial enrollment for all patients in all decision nodes. Supportive care (e.g., transfusion and antimicrobials as needed) for all patients (ICT for lower risk). Risk stratification supplemented by molecular testing.



https://ascopubs.org/doi/full/10.1200/EDBK_320113

MDS treatment strategies

- RARS has 75 month median survival.
- RCMD and RCMD-RS have 25 month median survival.
- Poor prognostic factor is hemoglobin <8g/dl, suggesting transfusion dependence.
- Multiple transfusions lead to iron overload
- Iron overload (ferritin >1000ng/ml) is also poor prognostic factor.
- Chelation required
- Multiple transfusions lead to alloimmunization.

MDS treatment strategies

- Must produce erythropoietin for administration of erythropoietin to be beneficial.
- May stimulate tumor growth, however
- Higher risk of thrombosis.
- Intensive antileukemic therapy show 60% complete remission rate (better in patients <50yo)
- t(8,21), inv16 had 100% CR
- Allogeneic bone marrow transplant
- 50% 3yr, 33% 4yr survival

MDS treatment strategies

- Lenalidomide preferred for del 5q.
- Hypomethylating agent azacitidine useful in high risk myelodysplastic syndrome.
- 48% of patients respond.
- Synergistic with histone deacetylase inhibitor (valproate, weak inhibitor).
- Clofaribine yields 30% complete remissions. Renal failure a risk.
- Thrombocytopenia a common outcome of therapy.
- Allogenic bone marrow transplantation may be curative.

EVIDENCE BLOCKS FOR THE TREATMENT OF PRIMARY MF OR POST-PV OR POST-ET MF

Lower-Risk (MF-1)	
Useful in certain circumstances	
Ruxolitinib	
Peginterferon alfa-2a	
Hydroxyurea	

Higher Risk (MF-2)			
Useful in certain circumstances			
	Transplant candidate	Non-transplant candidate; first-line therapy	Second-line therapy for patients previously treated with ruxolitinib
Ruxolitinib			—
Fedratinib			

EVIDENCE BLOCKS FOR THE MANAGEMENT OF MF-ASSOCIATED ANEMIA

Serum EPO <500 mU/mL

First-Line Therapy (MF-4)	
Darbepoetin alfa	
Epoetin alfa	
Second-Line Therapy (MF-4)	
Useful in certain circumstances	
Danazol	
Lenalidomide	
Lenalidomide/prednisone	
Thalidomide	
Thalidomide/prednisone	

Treatment of disease-related symptoms	
Ruxolitinib	
Fedratinib	

Serum EPO ≥500 mU/mL

Useful in certain circumstances	
Danazol	
Lenalidomide	
Lenalidomide/prednisone	
Thalidomide	
Thalidomide/prednisone	

RISK STRATIFICATION FOR PATIENTS WITH PMF

DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)[1]

Prognostic Variable	Points		
	0	1	2
Age, y	≤65	>65	
White blood cell count, x10^9/L	≤25	>25	
Hemoglobin, g/dL	≥10		<10
Peripheral blood blast, %	<1	≥1	
Constitutional symptoms, Y/N	N	Y	

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1 or 2
Intermediate-2 (INT-2)	3 or 4
High	5 or 6

DIPSS-PLUS[2]

Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement.

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION-ENHANCED IPSS (MIPSS-70) FOR PATIENTS WITH PMF AGE ≤70 YEARS[3]

Prognostic Variable	Points
Hemoglobin <10 g/dL	1
Leukocytes >25 x 10^9/L	2
Platelets <100 x 10^9/L	2
Circulating blasts ≥2%	1
Bone marrow fibrosis grade ≥2	1
Constitutional symptoms	1
CALR type-1 unmutated genotype	1
High-molecular risk (HMR) mutations[a]	1
≥2 HMR mutations	2

Risk Group	Points
Low	0–1
Intermediate	2–4
High	≥5

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION AND KAROTYPE-ENHANCED IPSS (MIPSS-70+ VERSION 2.0) FOR PATIENTS WITH PMF[4,5]

Prognostic Variable	Points
Severe anemia (Hemoglobin <8 g/dL in women and <9 g/dL in men)	2
Moderate anemia (Hemoglobin 8–9.9 g/dL in women and 9–10.9 g/dL in men)	1
Circulating blasts ≥2%	1
Constitutional symptoms	2
CALR type-1 unmutated genotype	2
HMR mutations[a]	2
≥2 HMR mutations	3
Complex karyotype[b]	3
Very-high-risk (VHR) karyotype[c]	4

Risk Group	Points
Very low	0
Low	1–2
Intermediate	3–4
High	5–8
Very high	≥9

IIPSS-70+ Version 2.0 can
.mipss70score.it/.

RISK STRATIFICATION FOR PATIENTS WITH POST-PV AND POST-ET MF

MYELOFIBROSIS SECONDARY TO PV AND ET-PROGNOSTIC MODEL (MYSEC-PM)[6]

Prognostic Variable	Points
Age at diagnosis	0.15 per patient's year of age
Hemoglobin <11 g/dL	2
Circulating blasts ≥3%	2
CALR-unmutated genotype	2
Platelets <150 x 10^9/L	1
Constitutional symptoms	1

Risk Group	Points
Low	<11
Intermediate-1 (INT-1)	≥11
Intermediate-2 (INT-2)	≥14 and <16
High	≥16

EVIDENCE BLOCKS FOR THE TREATMENT OF POLYCYTHEMIA VERA

Management of Vascular Symptoms

Regimen	Low-Risk (PV-1)	High-Risk (PV-2)
Aspirin		

	Low-Risk		High-Risk	
	First-Line Therapy (PV-1)	Second-Line Therapy (PV-1)	First-Line Therapy (PV-2)	Second-Line Therapy (PV-2)
Preferred regimens				
Hydroxyurea		—		—
Peginterferon alfa-2a		—		—
Ruxolitinib	—		—	
Other recommended regimens				
Hydroxyurea	—		—	
Peginterferon alfa-2a	—		—	
Useful in certain circumstances				
Busulfan (PO; especially for older adults)	—	—	—	

EVIDENCE BLOCKS FOR THE TREATMENT OF ESSENTIAL THROMBOCYTHEMIA

Management of Vascular Symptoms

Regimen	Very Low-Risk or Low-Risk (ET-1)	Intermediate-Risk (ET-2)	High-Risk (ET-3)
Aspirin			

	Very Low-Risk or Low-Risk		Intermediate-Risk		High-Risk	
	First-Line Therapy (ET-1)	Second-Line Therapy (ET-1)	First-Line Therapy (ET-2)	Second-Line Therapy (ET-2)	First-Line Therapy (ET-3)	Second-Line Therapy (ET-3)
Preferred regimen						
Hydroxyurea						
Other recommended regimens						
Peginterferon alfa-2a						
Anagrelide						
Useful in certain circumstances						
Ruxolitinib	—	—	—	—	—	
Busulfan (PO; especially for older adults)	—	—	—	—	—	

PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

Mutated Gene	Primary Myelofibrosis (PMF)
JAK2 V617F	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation[1]
MPL W515L/K	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation[1]
CALR	Improved survival compared to *JAK2* mutation and "triple-negative" PMF[1-4] Lower risk of thrombosis compared to *JAK2* mutation[1]
CALR Type 1/Type 1-like	Improved overall survival (OS) compared to *CALR* type 2/type 2-like and *JAK2* V617F mutation[5-8]
"Triple Negative" (non-mutated *JAK2, MPL, and CALR*)	Inferior leukemia-free survival compared to patients with *JAK2*- and/or *CALR*-mutated PMF[1-3] Inferior OS compared to patients with *CALR*-mutated PMF[2]
ASXL1	Independently associated with inferior OS* and leukemia-free survival as well as lower progression-free survival (PFS) following HCT [9,10]
EZH2	Independently associated with inferior OS[9]
IDH1/2	Independently associated with inferior leukemia-free survival as well as lower PFS following HCT [9,10]
SRSF2	Independently associated with inferior OS and leukemia-free survival[9]
Combined *CALR* and *ASXL1* status	Survival longest for *CALR*(+)*ASXL1*(-) patients (median 10.4 years) and shortest in *CALR*(-)*ASXL1*(+) patients (median 2.3 years)**[11] Intermediate survival (median 5.8 years) for *CALR*(+)*ASXL1*(+) or *CALR*(-)*ASXL1*(-) patients[11]
TP53	Associated with leukemic transformation[12]
U2AF1 Q157	Inferior OS compared to patients with *U2AF1* S34 mutated or *U2AF1* unmutated PMF. The effect was most evident in younger patients[13]
U2AF1 or *DNMT3A* or *CBL*	Associated with worse OS in patients with MF undergoing allogeneic HCT[14,15]

*_ASXL1_ mutation retains prognostic significance for inferior overall survival independent of IPSS or DIPSS-Plus risk score.
**The _CALR/ASXL1_ mutation status was DIPSS-Plus independent ($P < .0001$) and effective in identifying low-/intermediate-1-risk patients with shorter (median, 4 years) or longer (median 20 years) survival and high-/intermediate-2-risk patients with shorter (median, 2.3 years) survival.

Continued

PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN[1]

Mutated Gene	Polycythemia Vera (PV)
ASXL1/SRSF2/ IDH1/2/RUNX1	The presence of at least 1 of these "adverse variants/mutations" is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age, IWG prognostic model for PV, and karyotype.[2,3] Adverse variants/mutations also affected myelofibrosis-free survival (*ASXL1*) and leukemia-free survival (*IDH2* and *RUNX1*)[2,3]
JAK2 exon 12 mutation	Patients with *JAK2* exon 12-mutated PV exhibit younger age, increased mean hemoglobin/hematocrit, and lower mean white blood cell and platelet counts at diagnosis compared to those with *JAK2* V617F-mutated PV. However, both *JAK2* mutations are associated with similar rates of thrombosis, evolution to myelofibrosis or leukemia, and death.[4,5]

PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN[1]

Mutated Gene	Essential Thrombocythemia (ET)
CALR	Lower risk of thrombosis compared to *JAK2*-mutated ET[2-4] No difference in overall survival or myelofibrotic or leukemic transformation compared to *JAK2*-mutated ET[2-4] *CALR* mutation does not modify the IPSET score for predicting thrombosis in patients with ET[5]
TP53	Associated with inferior leukemia-free survival in multivariate analysis[6]
SH2B3/IDH2/U2AF1/ SRSF2/SF3B1/ EZH2/TP53/RUNX1	The presence of at least 1 of these "adverse variants/mutations" is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age and karyotype[7,8] Adverse variants/mutations also affect myelofibrosis-free survival (*U2AF1* and *SF3B1*) and leukemia-free survival (*EZH2* and *RUNX1*)[7,8]

RISK STRATIFICATION BY GENETICS IN NON-APL AML[1,2]

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

EVIDENCE BLOCKS FOR AML TREATMENT (AGE <60 YEARS)

RISK STATUS	POST-REMISSION THERAPY
Core binding factor (CBF) cytogenetic translocations without *KIT* mutation	HiDAC 3 g/m² over 3 h every 12 h on days 1, 3, 5 or days 1, 2, 3 x 3–4 cycles
	HiDAC 3 g/m² over 3 h every 12 h on days 1, 3, 5 or days 1, 2, 3 x 3–4 cycles + gemtuzumab ozogamicin 3 mg/m² (up to one 4.5 mg vial) on day 1 x 2 cycles (CD33-positive)
	Cytarabine 1000 mg/m² every 12 hours on days 1–4 + daunorubicin 60 mg/m² on day 1 (first cycle) or days 1–2 (second cycle) + gemtuzumab ozogamicin 3 mg/m² (up to one 4.5 mg vial) on day 1 x 2 cycles (CD33-positive)
Intermediate-risk cytogenetics and/or molecular abnormalities	HiDAC 1.5–3 g/m² over 3 h every 12 h on days 1, 3, 5 or days 1, 2, 3 x 3–4 cycles
	HiDAC 1.5–3 g/m² over 3 h every 12 h on days 1, 3, 5 or days 1, 2, 3 with oral midostaurin 50 mg every 12 hours on days 8–21 x 4 cycles (*FLT3*-mutated AML)
	Cytarabine 1000 mg/m² every 12 hours on days 1–4 + daunorubicin 60 mg/m² on day 1 (first cycle) or days 1–2 (second cycle) + gemtuzumab ozogamicin 3 mg/m² (up to one 4.5 mg vial) on day 1 x 2 cycles (CD33-positive)
Treatment-related disease other than CBF and/or unfavorable cytogenetics and/or molecular abnormalities	HiDAC 1.5–3 g/m² over 3 h every 12 h on days 1, 3, 5 or days 1, 2, 3 x 3–4 cycles
	HiDAC 1.5–3 g/m² over 3 h every 12 h on days 1, 3, 5 or days 1, 2, 3 with oral midostaurin 50 mg every 12 hours on days 8–21 x 4 cycles (*FLT3*-mutated AML)
	Dual-drug liposomal encapsulation of daunorubicin 29 mg/m² and cytarabine 65 mg/m² IV over 90 min on days 1 and 3 x 1–2 cycles (therapy-related AML or patients with antecedent MDS/CMML or AML-MRC) (preferred only if given in induction)

EVIDENCE BLOCKS FOR AML TREATMENT (AGE <60 YEARS)

TREATMENT STRATEGIES	INDUCTION REGIMENS
Favorable-risk cytogenetics	Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days and idarubicin 12 mg/m² x 3 days
	Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days and daunorubicin 60–90 mg/m² x 3 days
	Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and a single dose of gemtuzumab ozogamicin 3 mg/m² (up to one 4.5 mg vial) on day 1, or day 2, or day 3, or day 4; alternatively, three total doses on days 1, 4, and 7 (CD33-positive)
Intermediate-risk cytogenetics and *FLT3*-mutated (ITD or TKD)	Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and oral midostaurin 50 mg every 12 hours, days 8–21 (*FLT3*-mutated AML)
• Therapy-related AML other than CBF/APL • Antecedent MDS/CMML • Cytogenetic changes consistent with MDS (AML-MRC)	Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days and idarubicin 12 mg/m² x 3 days
	Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days and daunorubicin 60–90 mg/m² x 3 days
	Dual-drug liposomal encapsulation of daunorubicin 44 mg/m² and cytarabine 100 mg/m² IV over 90 min on days 1, 3, and 5 x 1 cycle
Other recommended regimens for intermediate- or poor-risk disease	Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days and idarubicin 12 mg/m² x 3 days
	Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days and daunorubicin 60–90 mg/m² x 3 days
	Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and cladribine 5 mg/m² x 5 days
	Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and a single dose of gemtuzumab ozogamicin 3 mg/m² (up to one 4.5 mg vial) on day 1, or day 2, or day 3, or day 4; alternatively, three total doses on days 1, 4, and 7 (CD33-positive/ intermediate-risk AML)
	High-dose cytarabine (HiDAC) 2 g/m² every 12 hours x 6 days or 3 g/m² every 12 hours x 4 days with idarubicin 12 mg/m² x 3 days (1 cycle)
	High-dose cytarabine (HiDAC) 2 g/m² every 12 hours x 6 days or 3 g/m² every 12 hours x 4 days with daunorubicin 60 mg/m² x 3 days (1 cycle)
	Fludarabine 30 mg/m² IV days 2–6, HiDAC 2 g/m² over 4 hours starting 4 hours after fludarabine on days 2–6, idarubicin 8 mg/m² IV days 4–6, and granulocyte colony-stimulating factor (G-CSF) subcutaneously (SC) daily days 1–7

THERAPY FOR RELAPSED/REFRACTORY DISEASE[1]

Clinical trial[1]

Targeted therapy:

- Therapy for AML with *FLT3*-ITD mutation
  - Gilteritinib[2] (category 1)
  - Hypomethylating agents (azacitidine or decitabine) + sorafenib[3,4]
- Therapy for AML with *FLT3*-TKD mutation
  - Gilteritinib[2] (category 1)
- Therapy for AML with *IDH2* mutation
  - Enasidenib[5]
- Therapy for AML with *IDH1* mutation
  - Ivosidenib[6]
- Therapy for CD33-positive AML
  - Gemtuzumab ozogamicin[7]

Aggressive therapy for appropriate patients:

- Cladribine + cytarabine + G-CSF ± mitoxantrone or idarubicin[8,9]
- HiDAC (if not received previously in treatment) ± (idarubicin or daunorubicin or mitoxantrone)
- Fludarabine + cytarabine + G-CSF ± idarubicin[10,11]
- Etoposide + cytarabine ± mitoxantrone[12]
- Clofarabine ± cytarabine + G-CSF ± idarubicin[13,14]

Less aggressive therapy:

- Hypomethylating agents (azacitidine or decitabine)
- Low-dose cytarabine (category 2B)
- Venetoclax + HMA/LDAC[15,16]

PRINCIPLES OF RADIATION THERAPY

I. General Principles

A. Patients who present with isolated extramedullary disease (myeloid sarcoma) should be treated with systemic therapy. Local therapy (radiation therapy [RT] or surgery [rare cases]) may be used for residual disease.

B. In a small group of patients where extramedullary disease is causing nerve compressions, a small dose of RT may be considered to decrease disease burden.

II. General Treatment Information

A. Dosing prescription regimen

1. CNS leukemia: RT[1] followed by IT chemotherapy[2] 2x/wk until clear, then weekly x 4–6 weeks[3]

AML treatment strategies

- Seven days of cytarabine and three days of anthracycline induction therapy for non-t(15;17) acute myelogenous leukemia leads to a complete remission in 81% of those CD34+ (41% if CD34-).
- Anthracycline vital if complete remission desired.
- If no remission after 14 days (bone marrow examination), induction repeated or high dose course of anthracycline, cytarabine, and amifostine begun.
- 25% 5 year survival; 7% treatment deaths.

AML treatment strategies

- For those younger than 60 years of age, consolidation with cytosine arabinoside follows complete remission.
- For those older than 60 years of age with minimal co-morbidity and favorable cytogenetics/molecular mutations, consolidation follows with a shorter course of cytosine arabinoside and idarubicin.
- Idarubicin less affected by P-glycoprotien pump
- May benefit from autologous stem cell rescue.
- Those with favorable risk may have 5 year survivals approaching 40%. Poor risk, <10%.

AML treatment strategies

- Addition of FLT3 inhibitors (e.g. midostaurin) to induction, consolidation and maintenance therapy in FLT3-mutated AML has recently shown promising results.
- Prevent thrombocytopenic hemorrhage (<10,000/dL) and control infection before AML induction
- Patients with leukocytosis at high risk for intracerebral hemorrhage; 600cGy in a single fraction with hydroxyurea for two days is emergency therapy
- Leukapheresis not more effective
- Begin allopurinol 1-2 days before therapy
- Hematologic growth factors may be harmful in priming

AML treatment strategies

- Allogeneic marrow transplant if intermediate or high risk patient though 25% mortality rate.
- Transplantation without prior induction chemotherapy associated with similar outcomes as if having received induction chemotherapy.
- Relapsed disease poor prognosis.
- CNS relapse usually followed by systemic relapse.
- Azacitidine or demcitabine use in chromosome 7 abnormality has led to cytogenetic response.
- Low dose azacitidine offers significantly overall survival with fewer hospitalizations and infections than do conventional regimens in older patients.

AML treatment strategies

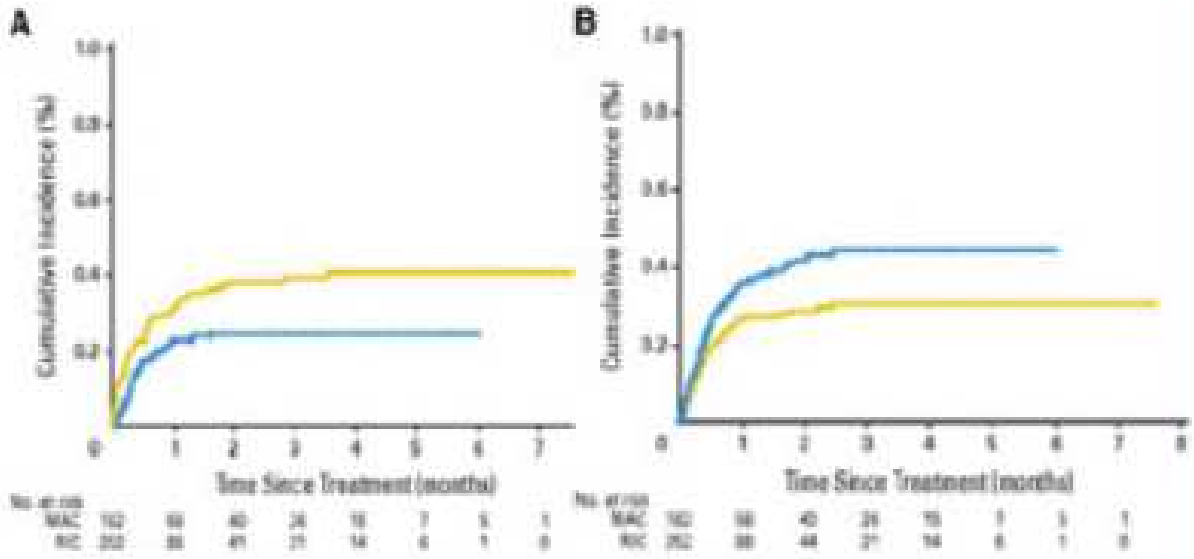
- Lenalidomide affects micro-vessel density. Induces tumor cell apoptosis directly through its effect on stromal support cells. Following azacitidine, lenalomide improves complete remission rate in older patients.
- Gemtuzumab ozogamicin (Anti-CD33 antibody conjugate) effective induction regimen in older patients with favorable or intermediate risk cytogenetics.

AML treatment strategies

- Quizartinib is an FTL3 kinase inhibitor.
- Volaserib is a polo-like kinase inhibitor (PLK1) with good responses across all genetic groups.
- Bortezomib, a proteasome inhibitor, with daunorubicin and cytosine arabinoside, an effective induction regimen in trials now underway.

AML treatment strategies

- Pregnant patient has fetus at risk in 1st trimester
- Alopecia, emesis, diarrhea universal
- Exfoliative keratitis,stomatitis common
- Spontaneously rising platelet count first sign of complete remission
- If post-treatment marrow shows residual leukemia without granulocytic maturation, re-examine in several days (common with anthracyclines)
- If platelet rise is transient and incomplete, generally failure; may be folate deficiency, particularly in elderly
- If only failure is thrombocytopenia, may respond to cyclosporin A



(A) Cumulative incidence of non-relapse mortality in patients ≥50 years of age receiving RIC (blue line) or MAC (gold line). Patients at risk treated with MAC or RIC at the different time intervals are given.

(B) Cumulative incidence of relapse (RIC –blue line; MAC – gold line).

Fig. 2.11

MAC, Myeloablative conditioning; RIC, reduced intensity conditioning.

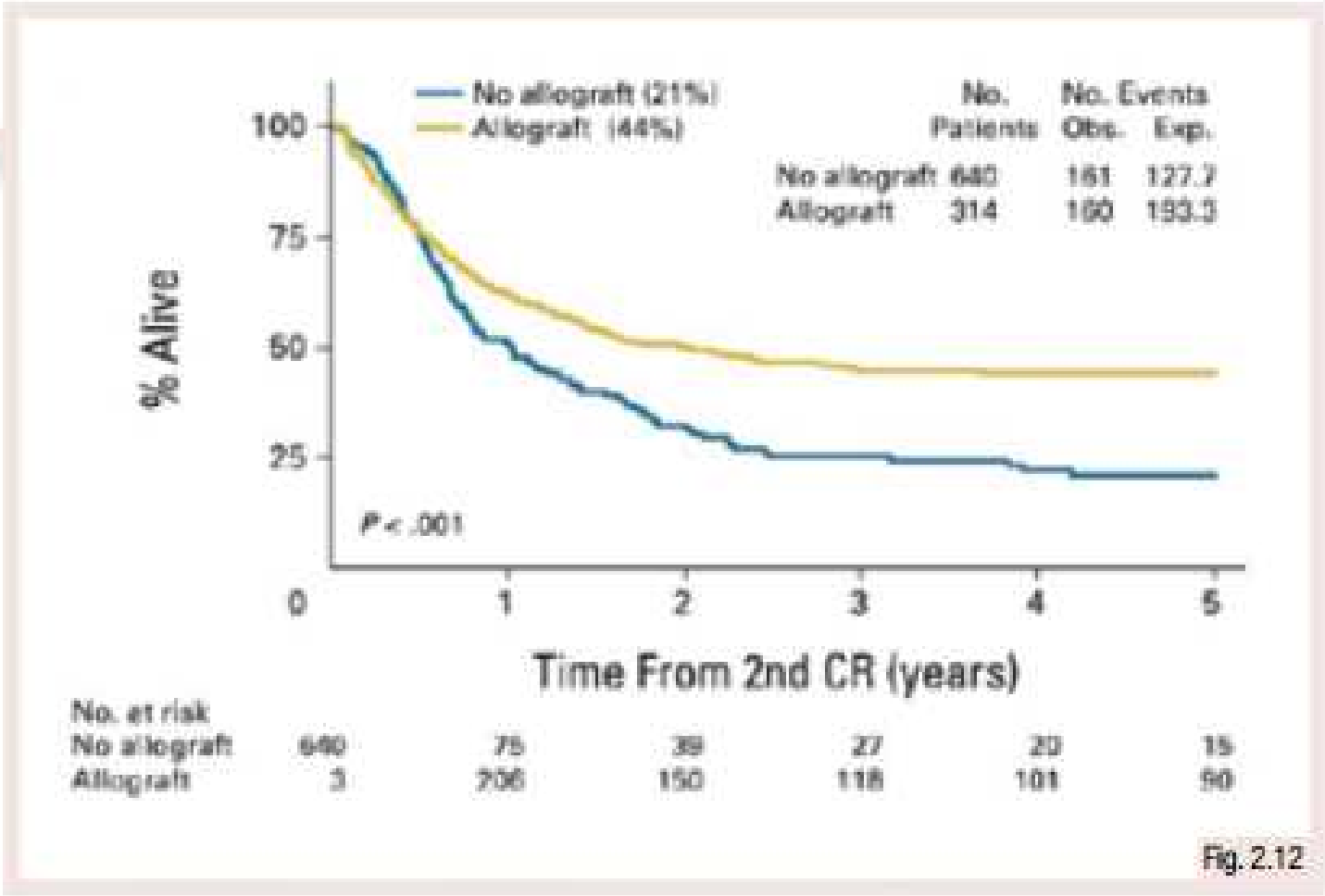
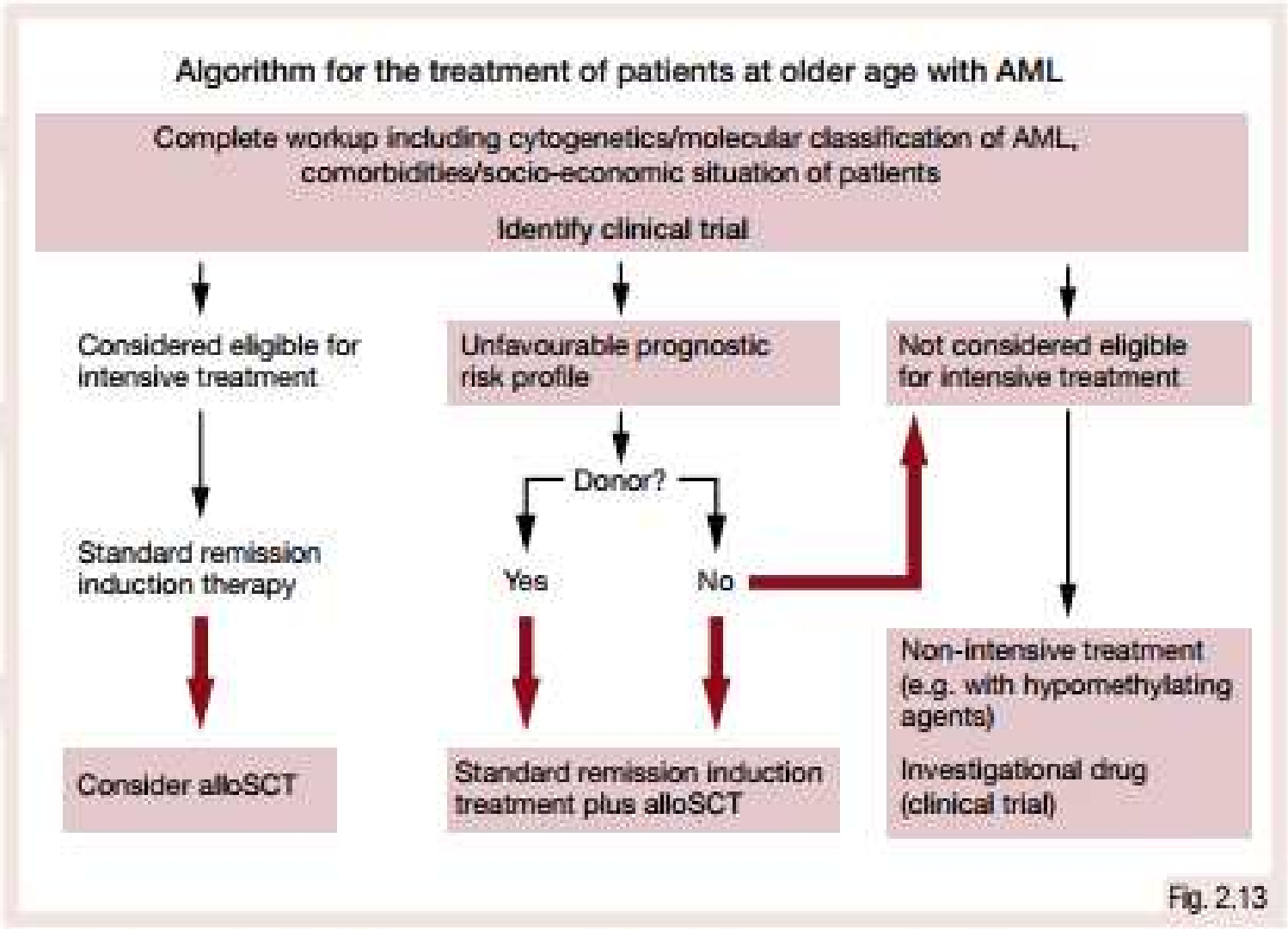


Fig. 2.12

CR, Complete response.



AlloSCT, Allogeneic stem cell transplantation; AML, acute myeloid leukaemia.

Refractory sideroblastic anemia

- Clinical management includes ESAs and/or transfusions to treat anemia, iron chelation (as established for low-risk MDS) in frequently transfused patients and low-dose aspirin (as established for essential thrombocytosis).

Low risk APL

WBC< 10,000 fl

Preferred Regimen
Induction: ATRA/arsenic trioxide; Consolidation: Arsenic trioxide/ATRA
Other Recommended Regimen
Induction: ATRA/idarubicin; Consolidation: ATRA/idarubicin, then ATRA/mitoxantrone, then ATRA/idarubicin

High risk APL

WBC> 10,000 fl

Preferred Regimens
Induction: ATRA/idarubicin/arsenic trioxide; Consolidation: ATRA/arsenic trioxide
Induction: ATRA/arsenic trioxide/gemtuzumab ozogamicin; Consolidation: Arsenic trioxide/ATRA
Induction: ATRA/arsenic trioxide/gemtuzumab ozogamicin; Consolidation: Gemtuzumab ozogamicin (if ATRA/arsenic trioxide discontinued due to toxicity)
Other Recommended Regimens
Induction: ATRA/daunorubicin/cytarabine; Consolidation: Arsenic trioxide, then ATRA/daunorubicin
Induction: ATRA/daunorubicin/cytarabine; Consolidation: Daunorubicin/cytarabine, then cytarabine/ daunorubicin/intrathecal chemotherapy
Induction: ATRA/idarubicin; Consolidation: ATRA/idarubicin/cytarabine, then ATRA/mitoxantrone, then ATRA/idarubicin/cytarabine

High risk APL

WBC> 10,000 fl
Cardiac issues

Induction: ATRA/arsenic trioxide/gemtuzumab ozogamicin; Consolidation: Arsenic trioxide/ATRA
Induction: ATRA/arsenic trioxide/gemtuzumab ozogamicin; Consolidation: Gemtuzumab ozogamicin (if ATRA/Arsenic trioxide discontinued due to toxicity)
Induction: ATRA/gemtuzumab ozogamicin; Consolidation: ATRA/gemtuzumab ozogamicin

Relapsed APL

Molecular or morphologic failure

Early Relapsed APL (<6 months) after ATRA and Arsenic Trioxide (No Anthracycline)
ATRA/idarubicin/arsenic trioxide; followed by ATRA/arsenic trioxide
ATRA/daunorubicin/cytarabine; followed by arsenic trioxide, then ATRA/daunorubicin
ATRA/daunorubicin/cytarabine; followed by daunorubicin/cytarabine, then cytarabine/daunorubicin/ intrathecal chemotherapy
ATRA/idarubicin; followed by ATRA/idarubicin/cytarabine, then ATRA/mitoxantrone, then ATRA/ idarubicin/cytarabine
No Prior Exposure to Arsenic Trioxide or Early Relapsed APL (<6 months) after ATRA and Anthracycline-C
Arsenic trioxide
Arsenic trioxide/ATRA
Arsenic trioxide/ATRA/gemtuzumab ozogamicin
Arsenic trioxide/gemtuzumab ozogamicin
Late Relapsed APL (≥6 months) after Arsenic Trioxide-Containing Regimen
Arsenic trioxide
Arsenic trioxide/anthracycline
Arsenic trioxide/ATRA
Arsenic trioxide/ATRA/anthracycline
Arsenic trioxide/ATRA/gemtuzumab ozogamicin
Arsenic trioxide/gemtuzumab ozogamicin
Additional Therapy after Second Morphologic Remission (If PCR-Negative and Not Transplant Candidate)
Arsenic trioxide x 6 cycles

APL treatment strategies

- Non-chemotherapy regimen of retinoic acid (ATRA) and arsenic trioxide effective in acute promyelocytic leukemia at low or intermediate risk.
- It is less toxic than chemotherapy.
- Relapsed disease is treated with arsenic trioxide until second complete remission (average, 35 days). 85% achieve complete remission.
- Stem cell transplantation with busulfan and cyclophosphamide consolidation is superior to conventional consolidation therapy in favorable and intermediate risk patients, especially if Minimal Residual Disease negative.

APL treatment strategies

- Induction therapy for high risk disease is (ATRA) daily until complete remission, combined with an anthracycline and cytarabine followed by allogenic stem cell therapy.
- Consolidation with alternating anthracycline/ anthracenedione (idarubicin, mitotranxone, idarubicin).
- Maintenance with daily ATRA, daily 6-mercaptopurine and weekly methotrexate.

APL syndrome
Retinoic acid syndrome

- Fever, dyspnea, pulmonary infiltrates, edema and effusions, renal dysfunction, and hypotension.
- Associated with rapidly rising neutrophil count.
- Capillary leak and cytokine release
- Seen in 20% of patients on ATRA induction or with arsenic trioxide induction.
- Manage with dexamethasone.
- Safe to use ATRA for maintenance once acute syndrome over.

APL treatment strategies

- Relapse is noted in 60-80% of cases of acute myelogenous leukemia post complete remission.
- If the relapse occurs before 6 months of remission, the prognosis is poor.
- Idarubicin and ATRA for relapse.

APL treatment strategies

- Reinduction is possible if relapse occurs >12 months post complete remission.
- Fludarabine and cytosine arabinoside with an anthracycline is associated with complete remission in 55% of patients.
- For relapsed acute promyelocytic leukemia, aresnic trioxide is administered daily to complete remission (average 35 days; 85% achieve).
- Arsenic trioxide prolongs the QT interval and is also associated with neuropathy. 25% of patients develop APL syndrome.

Chronic phase CML

RISK SCORE	Preferred Regimens
Low-risk score	First-generation TKI
	Imatinib
	Second-generation TKI
	Bosutinib
	Dasatinib
	Nilotinib
Intermediate-risk score	Second-generation TKI
	Bosutinib
	Dasatinib
	Nilotinib
High-risk score	Second-generation TKI
	Bosutinib
	Dasatinib
	Nilotinib

BCR-ABL1

THERAPY	CONTRAINDICATED MUTATIONS[u]
Bosutinib	*T315I, V299L, G250E, or F317L*[v]
Dasatinib	*T315I/A, F317L/V/I/C,* or *V299L*
Nilotinib	*T315I, Y253H, E255K/V, F359V/C/I, or G250E*
Ponatinib,[w] Omacetaxine,[x] allogeneic HCT (CML-6), or clinical trial	None

RISK CALCULATION TABLE

Risk Score	Calculation	Risk Category	
Sokal score[1]	Exp 0.0116 x (age - 43.4) + 0.0345 x (spleen - 7.51) + 0.188 x [(platelet count ÷ 700)^2 - 0.563] + 0.0887 x (blasts - 2.10)	Low Intermediate High	<0.8 0.8 – 1.2 >1.2
Hasford (EURO) score[2]	(0.6666 x age [0 when age <50 years; 1, otherwise] + 0.042 x spleen size [cm below costal margin] + 0.0584 × percent blasts + 0.0413 × percent eosinophils + 0.2039 × basophils [0 when basophils <3%; 1, otherwise] + 1.0956 × platelet count [0 when platelets <1500 × 10^5/L; 1, otherwise]) × 1000	Low Intermediate High	≤780 >780 – ≤1480 >1480
EUTOS long-term survival (ELTS) score[3]	0.0025 × (age/10)^3 + 0.0615 × spleen size cm below costal margin + 0.1052 × blasts in peripheral blood + 0.4104 × (platelet count/1000)$^{-0.5}$	Low Intermediate High	≤1.5680 >1.5680 but ≤2.2185 >2.2185

DEFINITIONS OF ACCELERATED PHASE[1,2]

Modified MD Anderson Cancer Center (MDACC) Criteria[3,4] (most commonly used in clinical trials)
• Peripheral blood myeloblasts ≥15% and <30% • Peripheral blood myeloblasts and promyelocytes combined ≥30% • Peripheral blood basophils ≥20% • Platelet count ≤100 x 10^9/L unrelated to therapy • Additional clonal cytogenetic abnormalities in Ph+ cells[5]

DEFINITIONS OF BLAST PHASE[1]

International Bone Marrow Transplant Registry[6,7]
• ≥30% blasts in the blood, marrow, or both • Extramedullary infiltrates of leukemic cells

CRITERIA FOR HEMATOLOGIC, CYTOGENETIC, AND MOLECULAR RESPONSE AND RELAPSE

Complete hematologic response[1]

- Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L
- Platelet count <450 x 10^9/L
- No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
- No signs and symptoms of disease with resolution of palpable splenomegaly

Cytogenetic response[2,3]

- Complete cytogenetic response (CCyR) - No Ph-positive metaphases[4]
- Major cytogenetic response (MCyR) - 0%–35% Ph-positive metaphases
- Partial cytogenetic response (PCyR) - 1%–35% Ph-positive metaphases
- Minor cytogenetic response - >35%–65% Ph-positive metaphases

Molecular response[5,6,7]

- Early molecular response (EMR) - *BCR-ABL1* (IS) ≤10% at 3 and 6 months
- Major molecular response (MMR) - *BCR-ABL1* (IS) ≤0.1% or ≥3-log reduction in *BCR-ABL1* mRNA from the standardized baseline, if qPCR (IS) is not available
- Deep molecular response (DMR) is defined as MR4.0: *BCR-ABL1* (IS) ≤0.01% or MR4.5: *BCR-ABL1* (IS) ≤0.0032%

Relapse

- Any sign of loss of response (defined as hematologic or cytogenetic relapse)
- 1-log increase in *BCR-ABL1* transcript levels with loss of MMR should prompt bone marrow evaluation for loss of CCyR but is not itself defined as relapse (eg, hematologic or cytogenetic relapse)

CML treatment strategies

- Imatinib, a tyrosine kinase inhibitor, induces cytogenetic responses in chronic myelogenous leukemia.
- It does not eliminate the cancer stem cell.
- Rise in histamine levels following imatinib therapy is a poor prognostic sign.
- Rapid BCR-ABL doubling time may indicate blast crisis (or cessation of therapy as a result of non-adherence).
- Long doubling times are typical with the emergence of BCR-ABL mutations in patients who maintain the chronic phase.

CML treatment strategies

- Approximately 86% of patients who achieve a complete cytogenetic response (loss of Ph chromosome) will not progress.
- However, 95% of those patients who achieve a major molecular response (loss of BCR-ABL) will not progress.
- If a complete molecular response is achieved within 6-12 months of therapy, 69% are likely to maintain that response as opposed to 37% of patients who require between 12 and i8 months to achieve that state.

CML treatment strategies

- Approximately 40% of patients who achieve a stable complete molecular response of at least 2 years duration can maintain the response following discontinuation of imatinib.
- Patients who are still BCR-ABL positive after 2 years of imatinib therapy are switched to nilotinib as it improves their chances of achieving a complete molecular response.
- T3151 mutation associated with resistance. Sunitinib (receptor tyrosine kinase inhibitor) employed.
- Loss of Y chromosome associated with fewer responses but does not affect overall survival.

CML treatment strategies

- Allogeneic stem cell transplant may be curative in chronic phase.
- IFN-α induces cytogenetic responses; effective with cytarabine. (Less effective than imatinib). Eliminates cancer stem cell.
- Hydroxyurea may be used as a debulking agent prior to stem cell transplantation.
- 30% of those in blast phase are TdT or CD10 positive. May respond to ALL therapy.
- Lymphoid blast stage may respond to induction with vincristine, prednisone, and dasatinib.
- Allogenic stem cell transplant

PV treatment strategies

- Polycythemia vera patients generally present following a thrombotic or hemorrhagic event.
- Headache, weakness, epigastric distress, and pruritis may be present.
- Maintaining an hematocrit <45% decreases the incidence of thrombotic complications
- The initial event is fatal in 35% of cases.
- Phlebotomy and low dose aspirin are recommended for those younger than 60 years of age and without thrombocytosis.
- There is a risk of bleeding.

PV treatment strategies

- Allopurinol is reserved for those with hyperuricemia.
- JAK inhibitors are associated with high response rates
- Consider hydroxyurea (begin 15-20 mg/kg/d) in those >60 years old with a history of a previous thrombosis.
- High risk polycythemia vera patients are treated with hydroxyurea (but 6% yearly transformation rate).
- If compliance is a problem, ^{32}P administration should be considered.
- Hydroxyurea and ^{32}P are leukemogenic.

ET treatment strategies

- Risk stratification in essential thrombocythemia is primarily based upon factors that influence the occurrence of thrombotic complications.
- 20% present with major thrombotic events.
- Elevated white count associated with thrombosis risk.
- Low dose aspirin is recommended. There is a risk of bleeding.

ET treatment strategies

- Angrelide, a cAMP phosphodiesterase inhibitor, also functions to interfere with megakaryocyte proliferation and platelet production, and may be used successfully (but not with aspirin).
- High risk patients are treated with hydroxyurea (but 6% yearly transformation rate to leukemia).
- JAK inhibitors show promise.
- Allogeneic bone marrow transplantation may benefit younger patients with myelofibrosis.