



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Acute Leukemia, MDS, and MPNs

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Clinical Focus: ALL, AML, CML, BPDCN, MDS, and MPNs

Research Focus: ALL, BPDCN, CML, AML, novel therapeutics for acute leukemia

Disclosures

- **Advisory boards and consulting:** AbbVie, Astra Zeneca, Autolus, Jazz, KITE, Merck, Novartis, Pfizer, Servier, Syndax
- **Research funding to institute:** AbbVie, Novartis

Key Learning Objectives

- Understand the key features distinguishing acute leukemia and non-acute (chronic) myeloid leukemias
- Recognize hematologic abnormalities that warrant specialist evaluation for acute and non-acute (chronic) myeloid leukemias
- Understand principals features of classification, risk stratification, and management for acute and non-acute (chronic) myeloid leukemias

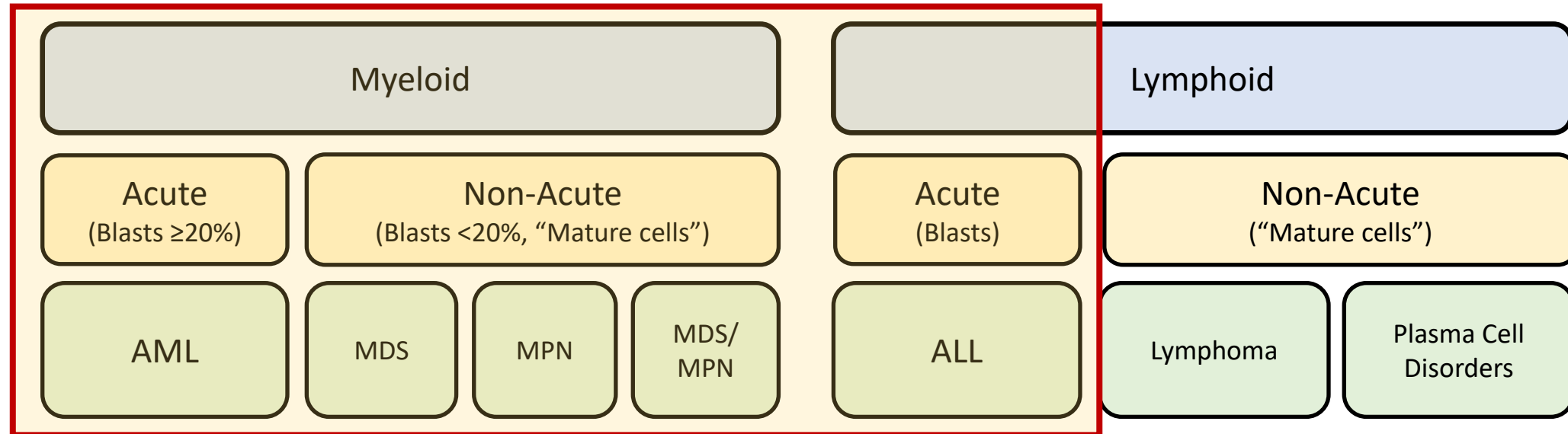
MOC Take Home Summary Statements

- **Acute leukemias are aggressive cancers of immature cells (“blasts”),** that develop over a short time frame.
 - **Key feature,** proliferation and differentiation impairment
 - **Diagnosis of acute leukemia** is made by confirming presence of blasts, and myeloid vs lymphoid lineage
 - **Acute promyelocytic leukemia (APL)** is a unique AML subtype characterized by early mortality due to coagulopathy, early recognition is critical
 - **Treatment of acute leukemia is focused on achieving and maintaining complete remission (CR),** with treatment tailored to leukemia subtype, risk (predicted sensitivity to treatment), and patient characteristics (age and comorbidities)
- **Non-acute myeloid leukemias are less aggressive myeloid lineage neoplasms,** that develop over a longer time frame
 - **Key feature,** no or less severe differentiation impairment (no or only mild increased in blasts)
 - **Diagnoses** categorized as myelo -dysplastic (MDS), -proliferative (MPNs), or MDS/MPN overlap syndromes:
 - MDS is characterized by dysplasia and cytopenias
 - MPNs are characterized by proliferation, and divided into Ph+ (CML) and Ph- subtypes
 - **Treatment** is focused on **managing symptoms of cytopenias or cytosis, reducing risk of thrombosis** in Ph-negative MPNs, and **reducing risk of progression in CML** (with TKIs) and **high risk MDS/Ph-neg MPNs** (with chemotherapy, transplant)

Outline

- **Acute Leukemia**
 - Acute myeloid leukemia (AML)
 - Acute lymphoblastic leukemia (ALL)
- **Chronic Myeloid Neoplasms**
 - Myelodysplastic syndromes (MDS)
 - Myeloproliferative disorders (MPN)
 - Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML)
 - Philadelphia chromosome-negative (Ph-) MPNs (classical – ET, PV, MF; non-classical)
 - MDS/MPN overlap syndromes

Hematologic malignancies framework

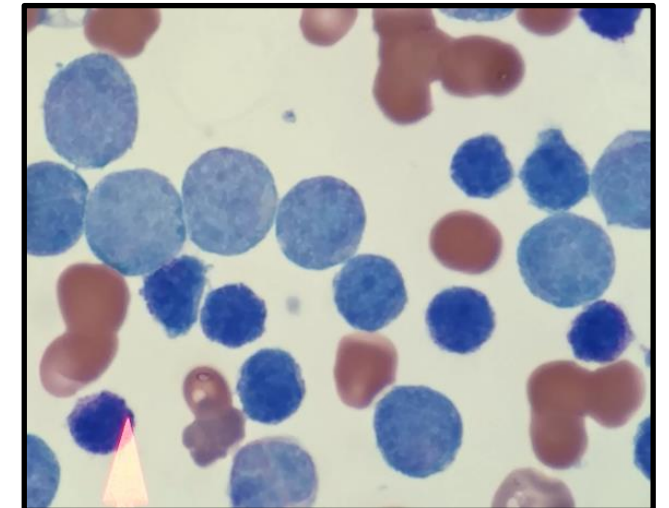
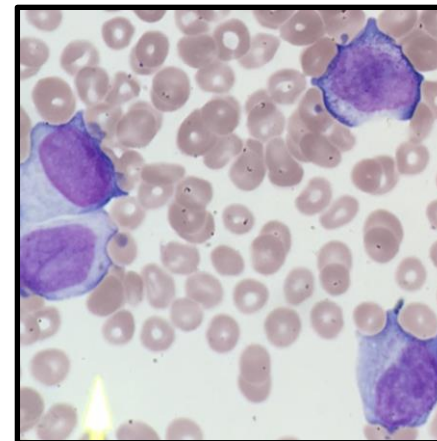
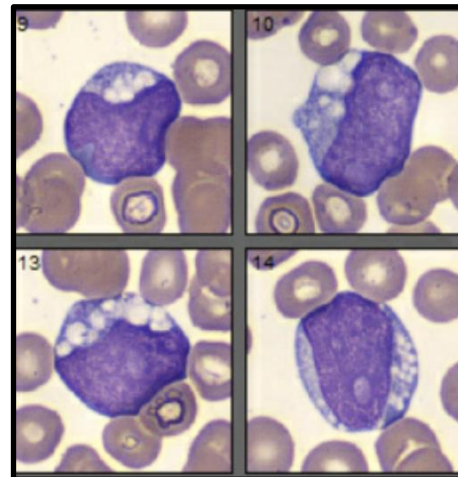
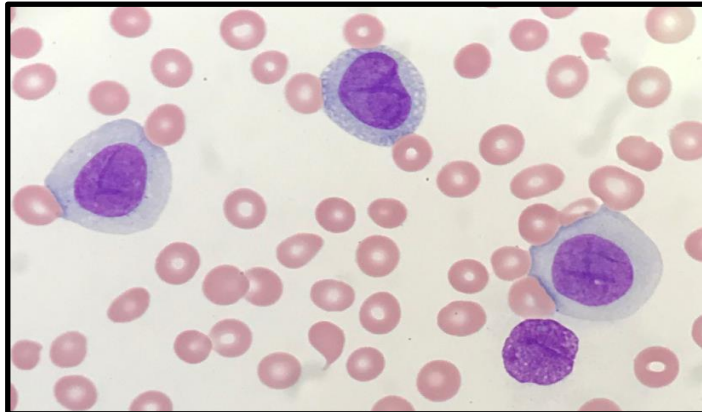
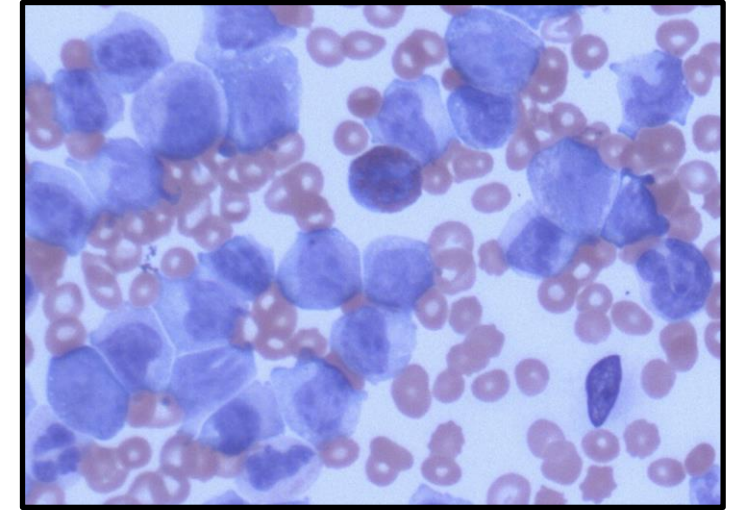
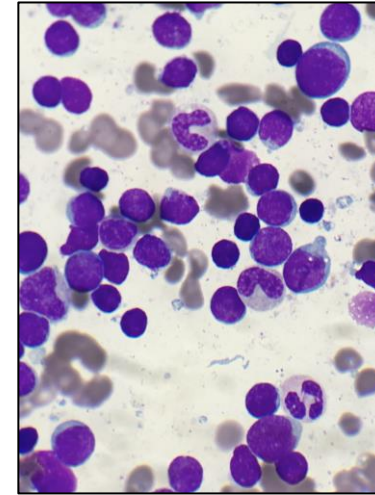
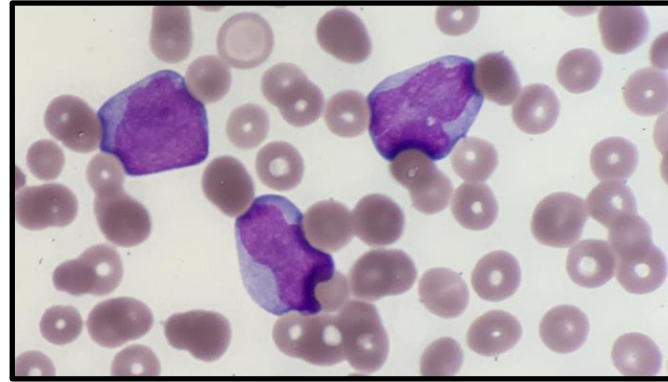
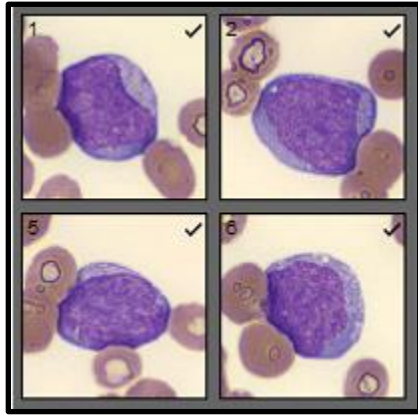


- **“Acute” leukemias** – Proliferation of immature cells (blasts) with impaired differentiation
- **“Non-Acute” myeloid leukemias (“chronic”), lymphomas, and plasma cell disorders** – Proliferation of differentiated myeloid and lymphoid cells with *less or no* impairment of differentiation

Note: Term “leukemia” refers to “circulating” disease (i.e. lymphomas can occur in “leukemic” phase)

Note: Term “lymphoma” refers to accumulation of disease in lymphoid structures (i.e. lymphoblastic lymphoma)

Blasts do not all look the same...



But there are morphologic clues....

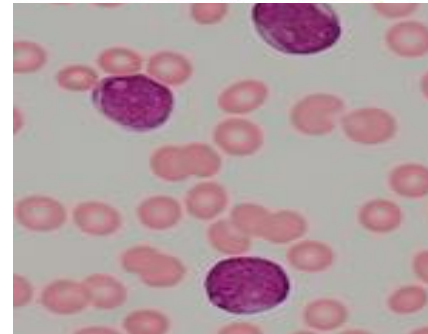
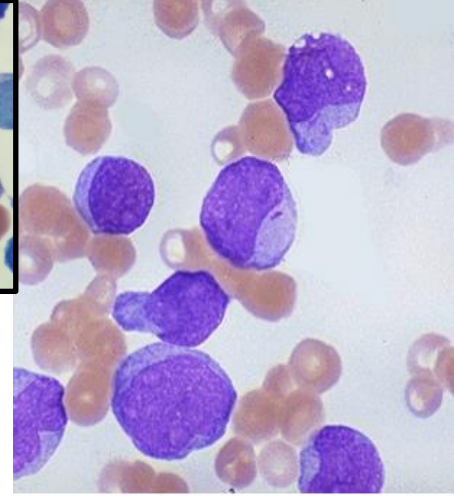
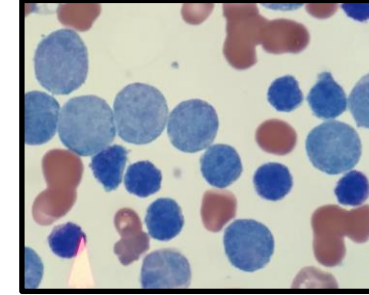
- **Identifying a blast (and therefore concern for leukemia...)**
 - **What are blasts?** Immature cells (remember: “b” for **b**aby)
 - **Morphology:** Large nuclei and scant cytoplasm (high N:C ratio); open chromatin, nucleoli
 - **Situational awareness:** Abnormalities in other cell lineages (cytopenias – neutropenia, anemia, thrombocytopenia; **monocytosis**)
- **Lineage of blasts (i.e. lymphoid versus myeloid)**
 - Myeloid – Auer rods (confirmatory), “monocytic-appearing”
 - Lymphoid – Smaller blasts with very little cytoplasm (look like lymphocytes)
 - **Confirmation:** Flow cytometry or immunohistochemistry to confirm developmental stage (“immature”) and lineage (myeloid vs lymphoid)
- **Fake outs:** Atypical lymphs (mononucleosis); lymphoma in “leukemic phase”

Blast immunophenotype

- **Immaturity:** CD34 (myeloid or lymphoid), TdT (lymphoid)
 - Not all blasts will express
- **Acute myeloid leukemia:**
 - **MPO**
 - Myeloid: CD13, CD33, CD117
 - Monocytic: NSE, lysozyme, CD11, CD14, CD64
- **Acute lymphoblastic leukemia:**
 - B-cell: CD10, **CD19**, CD20, CD22, (slg negative)
 - T-cell: CD2, **CD3**, CD7

Pearl: Can see “aberrant” expression of lineage markers

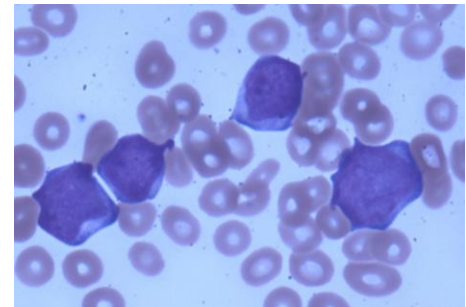
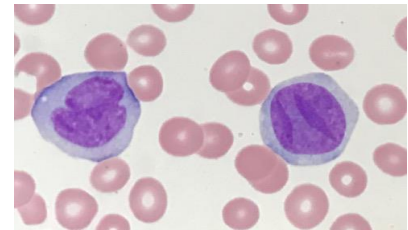
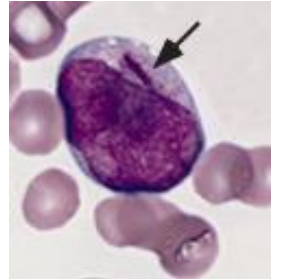
Lineage specific markers:
AML: **MPO**, or **2+ myeloid/ monocytic markers**
T-ALL: **CD3**
B-ALL: **CD19** + additional (CD10, CD22, CD79a, PAX5)



Acute Leukemia:
Are **blasts** $\geq 20\%$

Acute myeloid leukemia (AML) – Diagnosis

- **Myeloid blasts $\geq 20\%$** of total cells of bone marrow aspirate, leukemic blood, or other tissue
 - Disease MAY be “extra-medullary” (outside the marrow)
 - *Myeloid sarcoma = chloroma = granulocytic sarcoma*
 - Certain genetic drivers [t(8;21), inv(16), t(15;17), *NPM1*] = disease-defining regardless of blast number
- Blasts can be identified or suspected morphologically
- **Lineage (myeloid vs lymphoid) assignment requires additional tests** to confirm immunophenotype (flow cytometry, stains) unless **Auer rods** are present (indicates, myeloid)

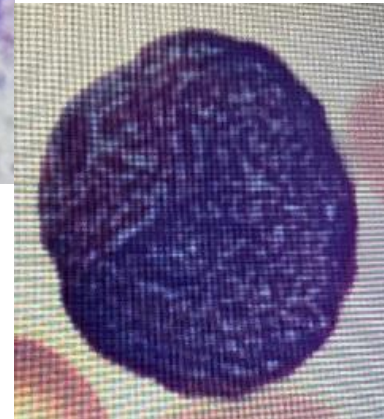
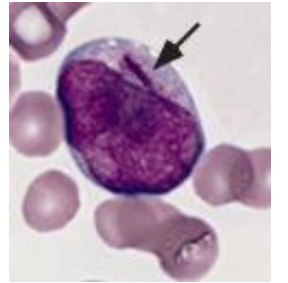
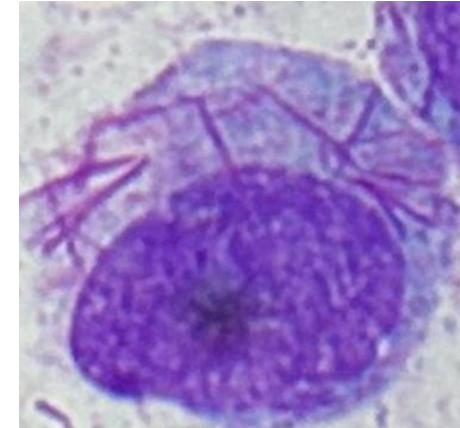
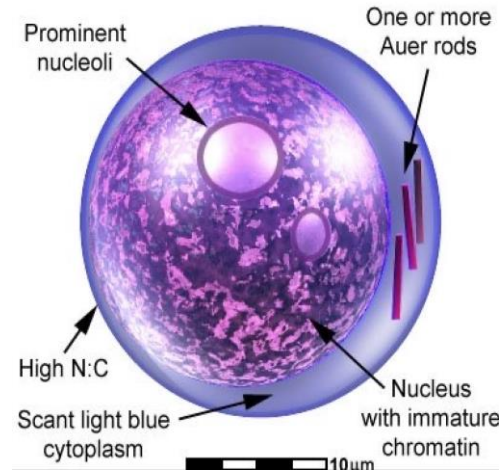
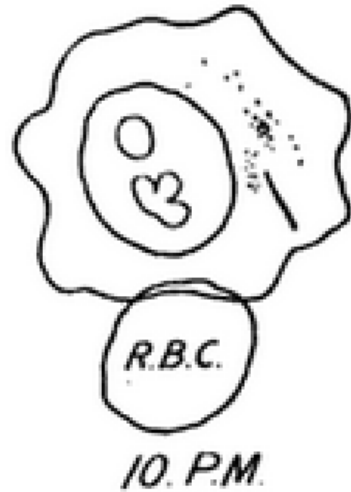
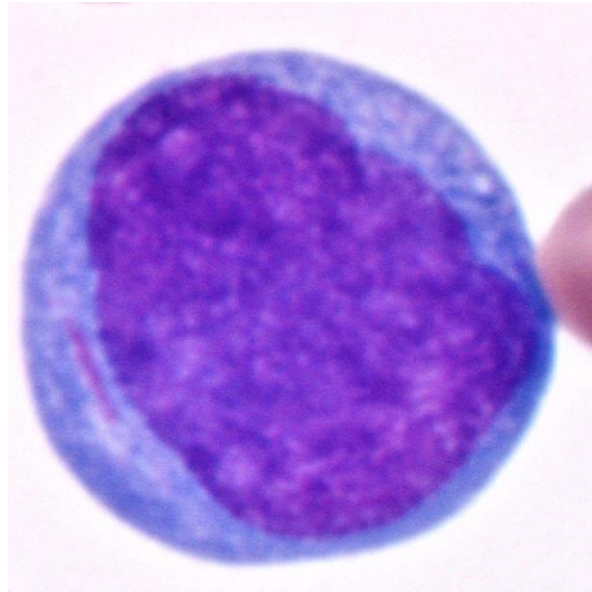


Auer rods

SOME HITHERTO UNDESCRIBED STRUCTURES FOUND IN THE LARGE LYMPHOCYTES OF A CASE OF ACUTE LEUKÆMIA.

BY JOHN AUER, M.D.,

FORMER HOUSE OFFICER OF THE JOHNS HOPKINS HOSPITAL; FELLOW OF THE ROCKEFELLER
INSTITUTE FOR MEDICAL RESEARCH.



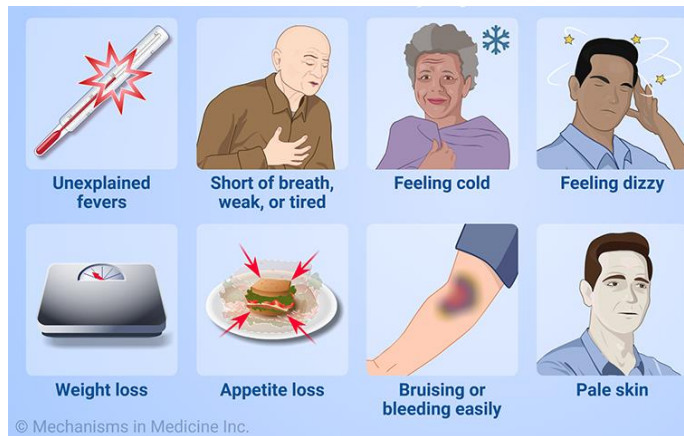
- John Auer (1875-1948) described in 1906 in a patient at Hopkins under William Osler
- Rod shaped crystalline structures from primary granules of myeloid blasts
- **Confirm myeloid lineage blasts (always abnormal); however, not always present**

Acute myeloid leukemia (AML) – Diagnosis

Acute: Increased immature, abnormal myeloid blasts (>20%), presenting “acutely”

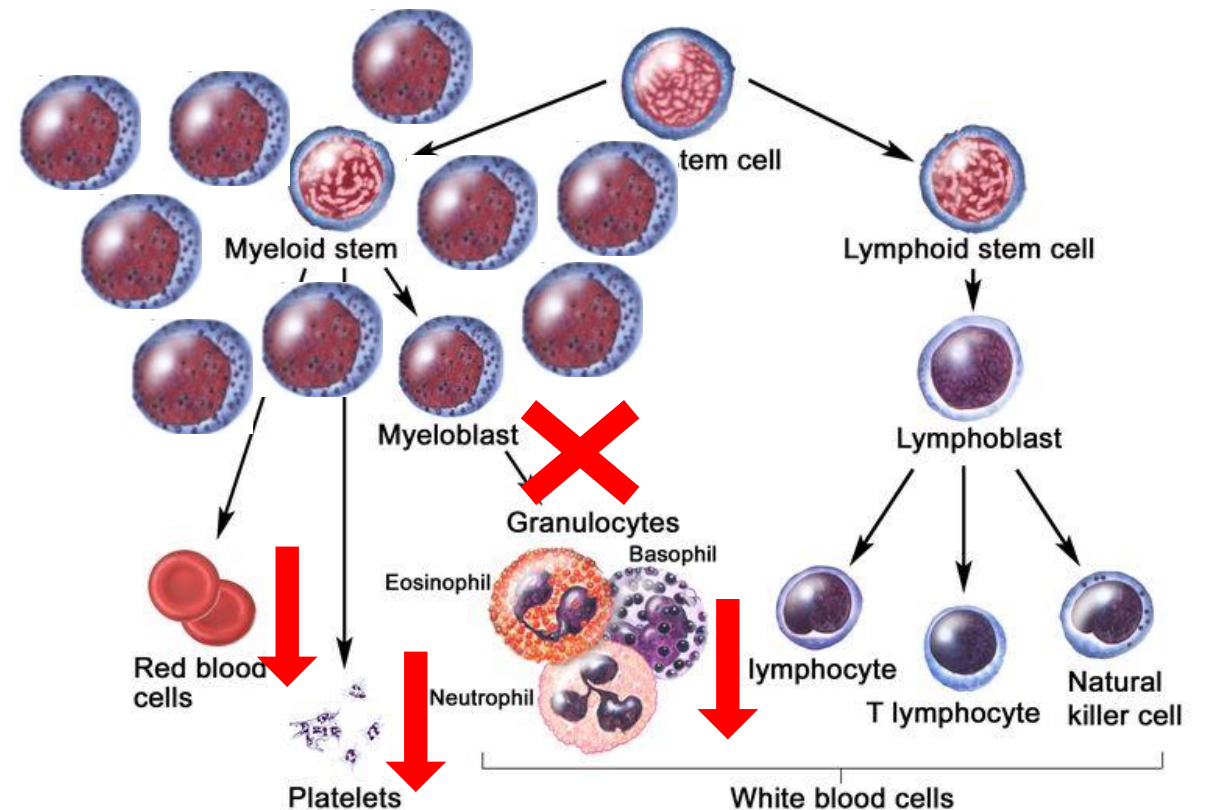
Myeloid: Originate in bone marrow (“myeloid compartment”)

Leukemia: Circulating disease



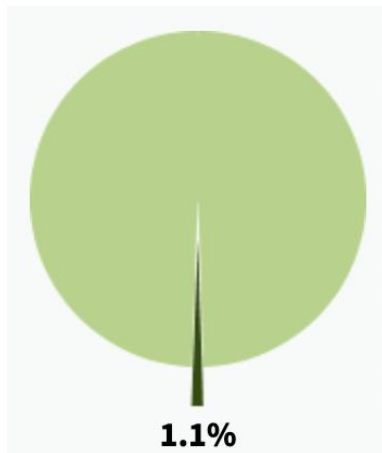
Develops over days to weeks

↓ **White blood cells** = ↑ infections
↓ **Red blood cells** = ↑ fatigue
↓ **Platelets** = ↑ bleeding/bruising

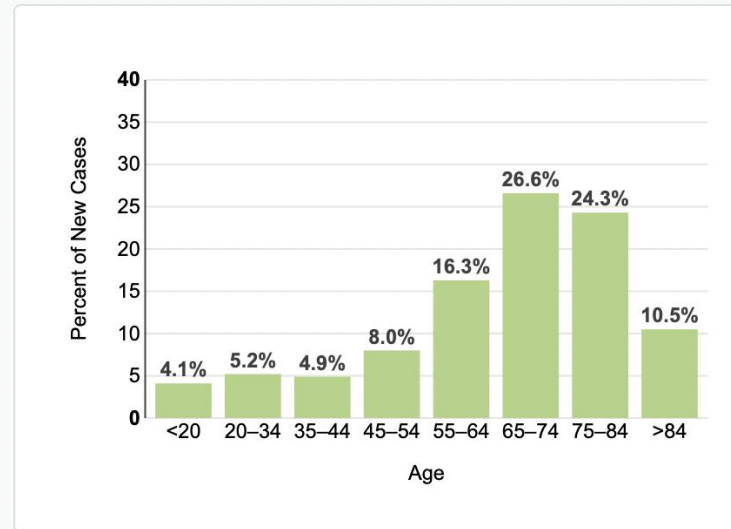


AML – Epidemiology

Estimated New Cases in 2025	22,010
% of All New Cancer Cases	1.1%



Percent of New Cases by Age Group: Acute Myeloid Leukemia



Acute myeloid leukemia is most frequently diagnosed among people aged 65–74.

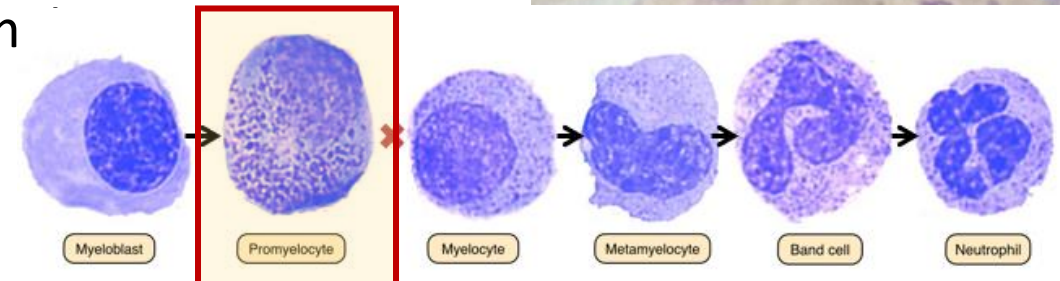
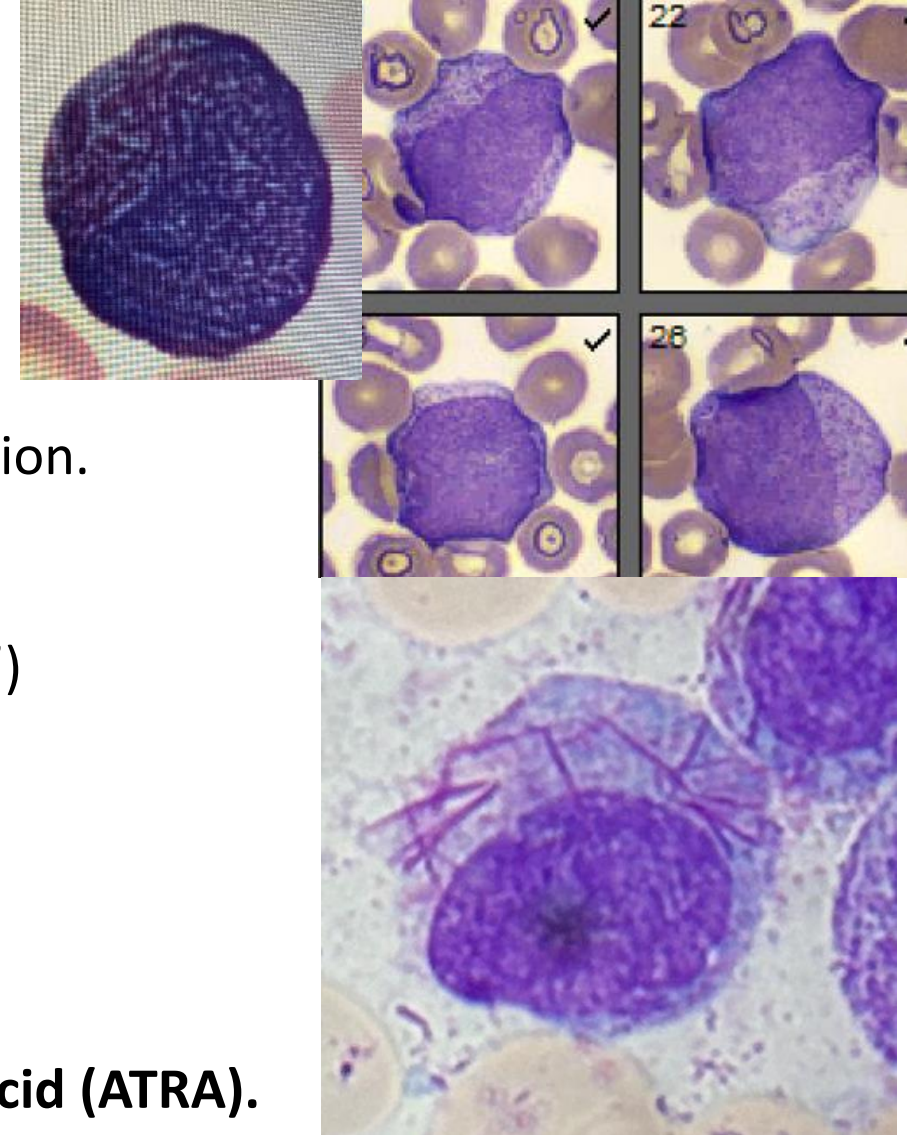
Median Age
At Diagnosis

69

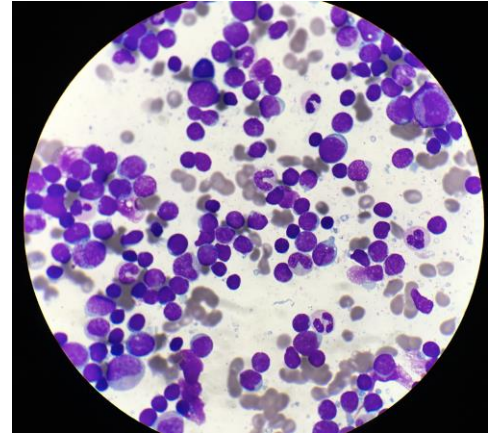
Risk factors: Age, radiation/chemotherapy, antecedent non-acute myeloid neoplasm, bone marrow failure (inherited, immune mediated)

Acute promyelocytic leukemia

- **RARE – MUST NOT MISS – DIAGNOSIS**
- AML subtype (~10%) defined by presence of **t(15;17)** translocation.
- Features:
 - Younger (but not always)
 - Pancytopenia; malignant promyelocytes (“blast equivalent”)
 - Coagulopathy: bruising, bleeding, low fibrinogen
- **HIGH EARLY MORTALITY** – Coagulopathy (CNS hemorrhage).
- **HIGH CURE RATES** – If survive acute phase, >95% cure rate.
- Confirm: Cytogenetics t(15;17); RT-PCR *PML-RARA*.
- Treat:
 - **Stabilize** – Transfuse (platelets, cryo, FFP), **all-trans retinoic acid (ATRA)**.
 - **Definitive** – **ATRA**, **arsenic**, chemotherapy, gemtuzum



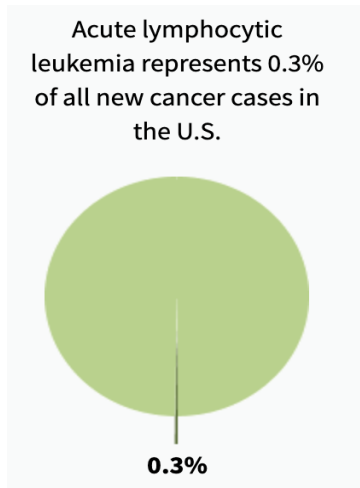
Acute lymphoblastic leukemia (ALL) – Diagnosis



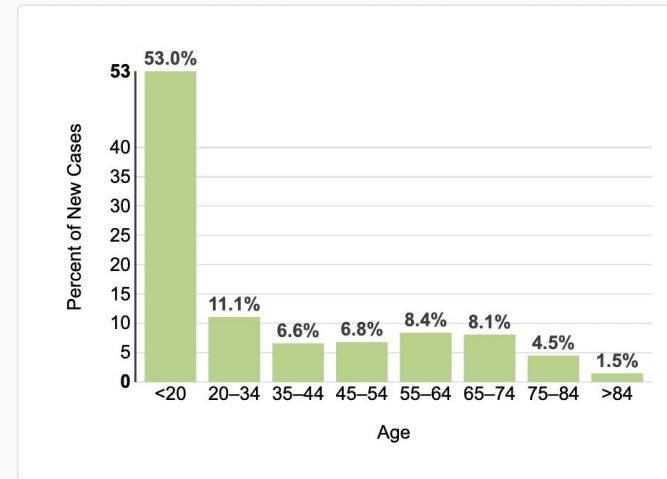
- **Aggressive hematologic neoplasm of B- or T-lymphoblasts**
 - Acute lymphoblastic leukemia (ALL) /Lymphoblastic lymphoma (LBL).
- **Clinical Presentation**
 - Cytopenias, **adenopathy, mediastinal mass (T-cell),**
hepatosplenomegaly, **central nervous system**
 - Constitutional (fatigue, fevers, sweats, weight loss, bone pain)
- **Diagnosis: Morphology (blasts), immunophenotype to confirm immature stage and determine lymphoid (B or T) lineage**

ALL – Epidemiology

Estimated New Cases in 2025	6,100
% of All New Cancer Cases	0.3%



Percent of New Cases by Age Group: Acute Lymphocytic Leukemia



Acute lymphocytic leukemia is most frequently diagnosed among people aged <20.

Median Age
At Diagnosis

17

- Most common leukemia in children
- Adults comprise ~50% of ALL diagnoses, but majority of deaths
- Risk factors: Down syndrome, prior chemo/radiation
- In adults, ~1/3 are Philadelphia chromosome-positive

Acute leukemia – approach to therapy

- **Induction Goal → Remission**

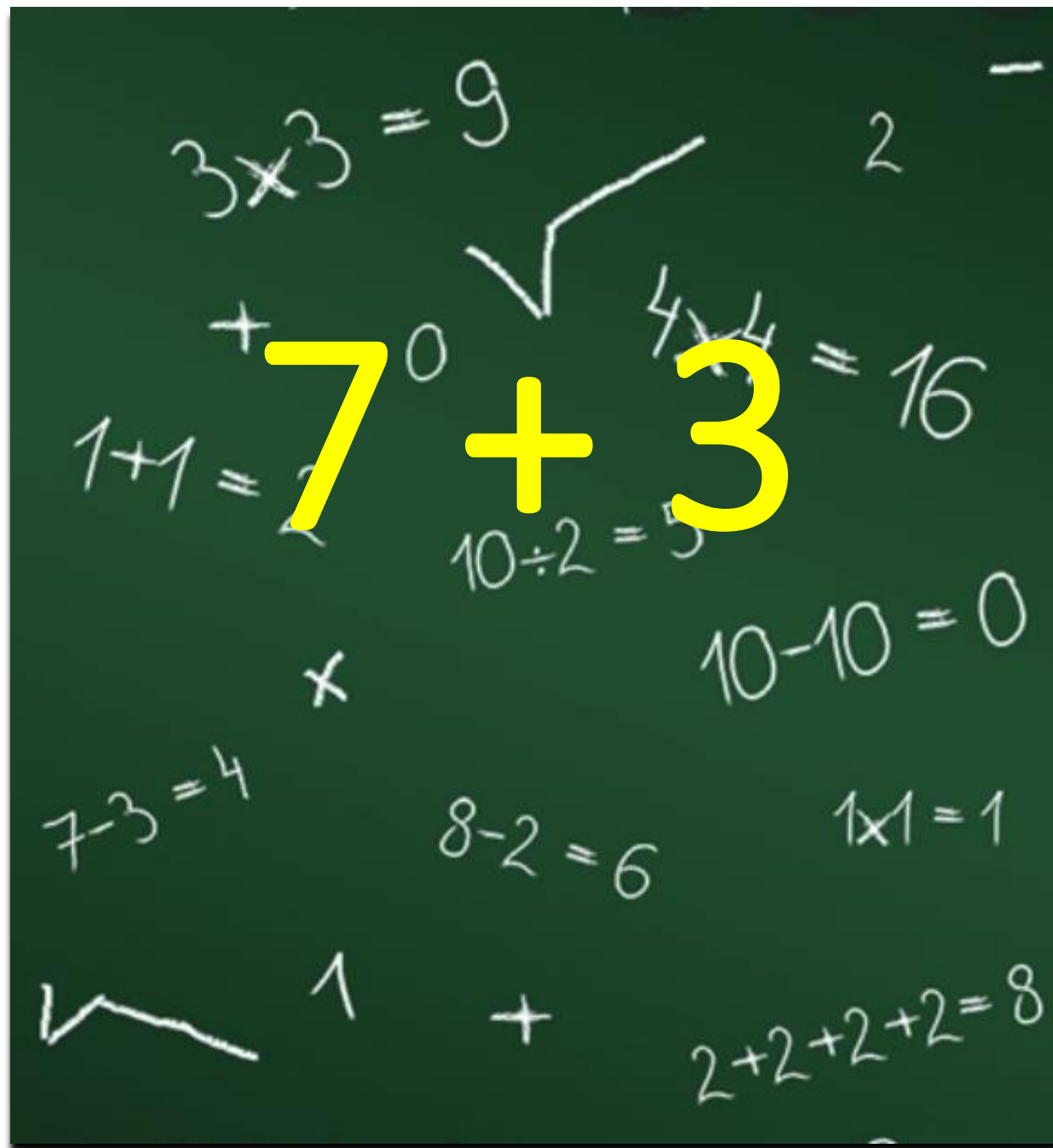
- Reduce disease to morphologically undetectable levels → complete remission (CR). No blasts in blood. Fewer than 5% blasts in marrow
- Ideally with recovery of “normal” blood counts

- **Consolidation Therapy Goal → Lengthen CR / Survival**

- **Cure**: Reduce residual disease to prevent relapse (“cure”)
- **Prolong remission/delay progression**: Maintain disease at a minimal residual disease state for as long as possible (extend survival, no cure)

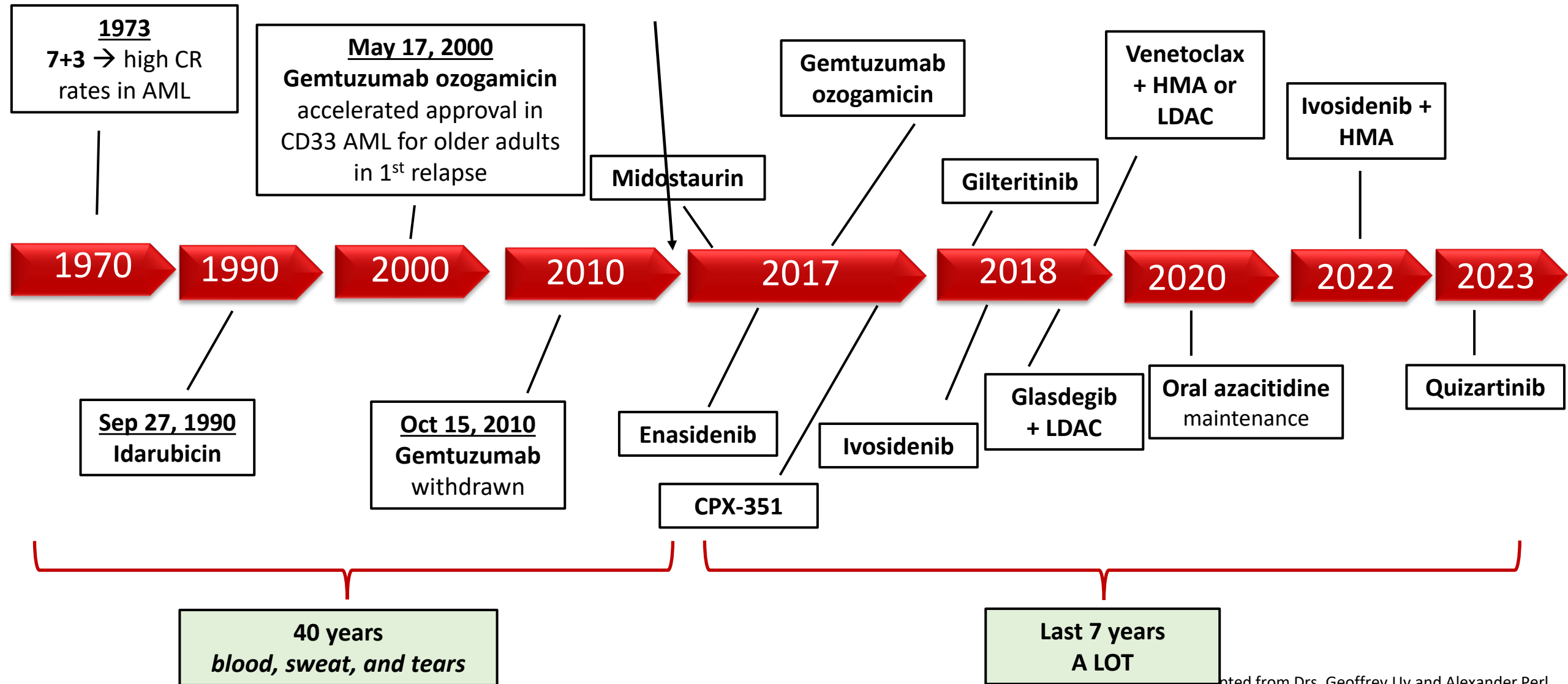
AML? Elementary!

That was then...



(Many) New FDA approved agents for AML

Marlise becomes Leukemia MD (2016)



AML – This is NOW (2026). **CHOICE!**

	Age < 60	Age 60-75 “fit older”	Age >75 or “unfit”
Intent	Curative (Regularly)	Curative (Sometimes)	Palliative
Initial Treatment (Induction)	daunorubicin + cytarabine (7+3) +/- midostaurin or quizartinib (<i>if FLT3</i>) +/- gemtuzumab ozogamicin (<i>if CBF</i>)	7+3 +/- mido, quiz, GO CPX-351 (<i>if</i> secondary, therapy-related) HMA + venetoclax	HMA + venetoclax HMA + ivosidenib Ivosidenib HMA (Enasidenib) Supportive care Hospice
Consolidation	<u>Favorable</u> : Cytarabine (HiDAC) <u>Non-Favorable</u> : Transplant (+/- FLT3 inhibitor)	<u>Chemo</u> Cytarabine Oral azacitidine HMA + venetoclax <u>Transplant</u> (+/- FLT3 inhibitor)	

AML – Prognostic features

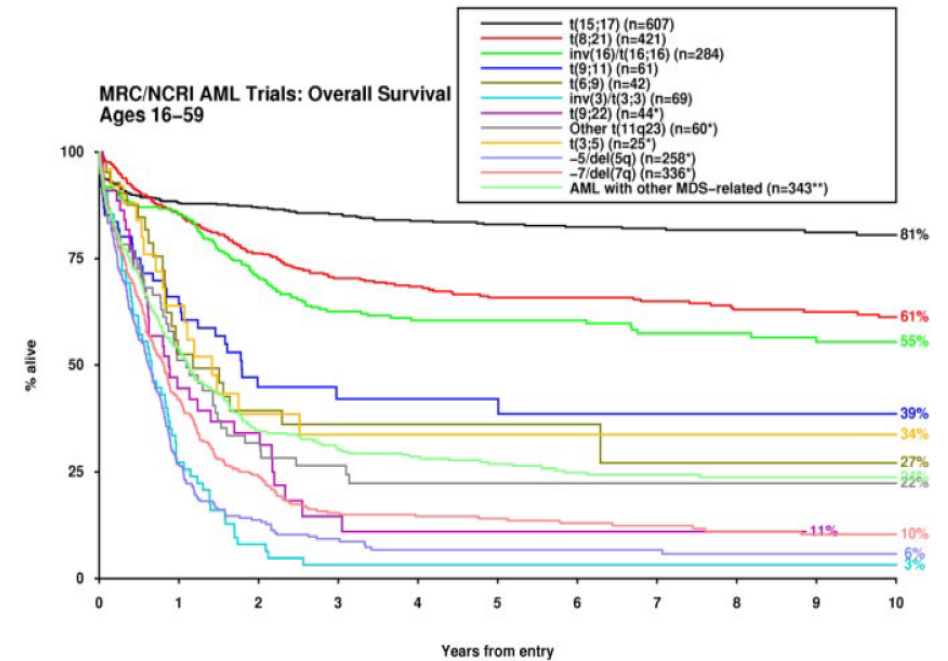
Age: Older

Disease “context” (clinical ontogeny)

- Favorable: De novo
- Unfavorable:
 - “Therapy-related” AML (prior chemotherapy/XRT)
 - “Secondary” AML (prior MDS/MPN)

Genetics (chromosomes and gene level mutations)

- Favorable:
 - *Chromosomes*: APL [t(15;17)]; “core binding factor” AML: t(8;21); inversion 16.
 - *Molecular*: *NPM1* mutant without *FLT3*-ITD, *CEBPA* bZIP in-frame mutated
- Unfavorable:
 - *Chromosomes*: Complex (3+), monosomal, 5 and 7 abnormality, inv 3, *KMT2A-r*, etc.
 - *Gene*: *TP53*; “secondary-type”



AML – Initial therapy

- **“Intensive” cytotoxic chemotherapy** – *fit, chemo-responsive AML*
 - Daunorubicin and cytarabine (“7+3”) – traditional AML induction
 - CPX-351 (Vyxeos) – liposomal daunorubicin/cytarabine – for “high risk”
- **“Less-intensive” chemotherapy** – *older, unfit, chemo-insensitive AML*
 - Hypomethylating agents (decitabine, azacitidine)
 - Plus venetoclax (BCL2 inhibitor), or targeted therapy
- **Targeted therapy**
 - Alone or in combination
 - FLT3 inhibitors, IDH inhibitors, menin inhibitors

AML – Consolidation / post-remission

- **Curative intent**
 - **Chemotherapy (high dose-cytarabine)** – “Fit” patients with “favorable” AML
 - **Allogeneic transplant** – “Fit” patients with “high-risk” AML (defined by age, ontogeny, genetics, prior treatment failure)
- **Non-curative intent**
 - Continue HMA-based or targeted chemotherapy

Hematopoietic stem cell transplantation

- **Allogeneic:** from another person
- **Concept:**
 - Conditioning chemotherapy to “make room” for donor cells and suppress immune system
 - Donor cells “engraft” and create new blood system (with new immune system) → graft-versus-leukemia (GvL)
 - Myeloablative (ablates marrow, more toxicity): relies on both chemo and GvL
 - Non-myeloablative / reduced intensity: relies on GvL
- **Risks:**
 - Chemotherapy toxicities
 - Immune suppression: Opportunistic infection
 - Graft versus host disease: Liver, skin, gastrointestinal

ALL – A pediatric oncology success story

- **1948:** Sidney Farber described 5 children who responded (temporarily) to the folic acid antagonist **aminopterin**

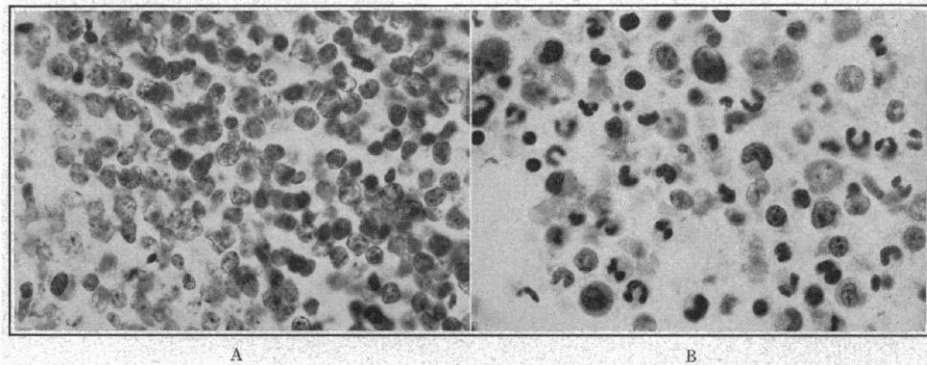
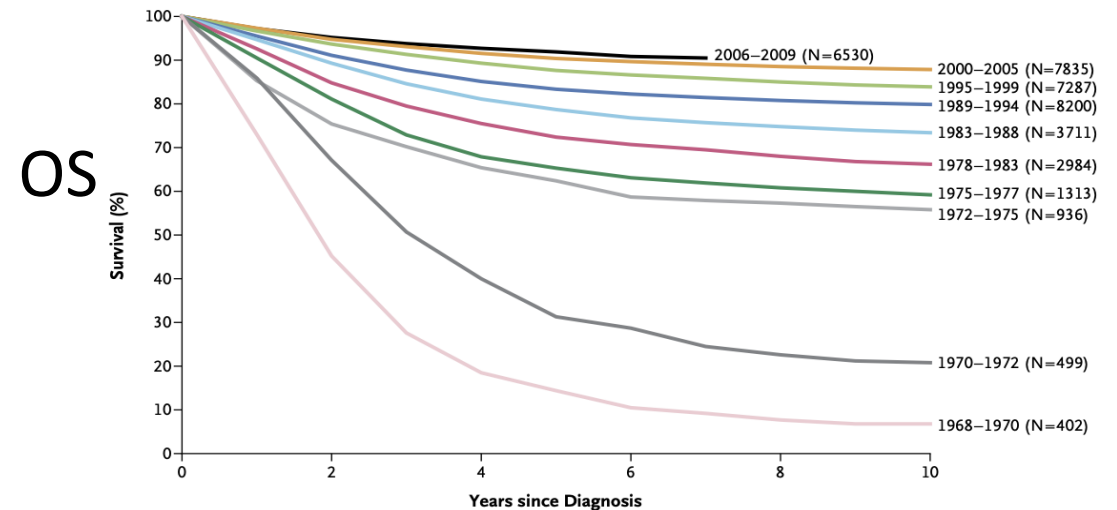


FIGURE 4. Photomicrographs of the Sternal Bone Marrow in Case 3, Showing Giemsa-Stained Section on January 29, (A) and April 3 (B), 1948 (x1000).
Note that the microscopical field is composed mainly of blast forms characteristic of leukemia (cell type undetermined) in the early section (A) and that a marked shift to mature cell forms, particularly of the polymorphonuclear series, with no leukemic cells, had occurred on the later examination (B).



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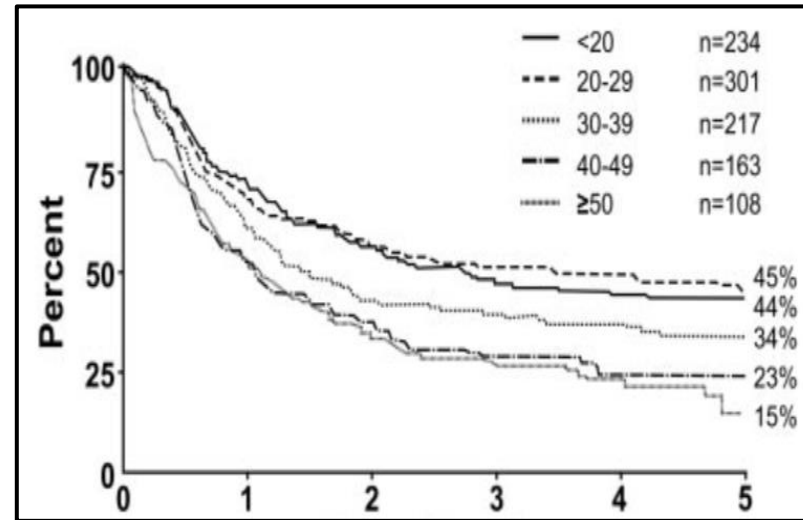
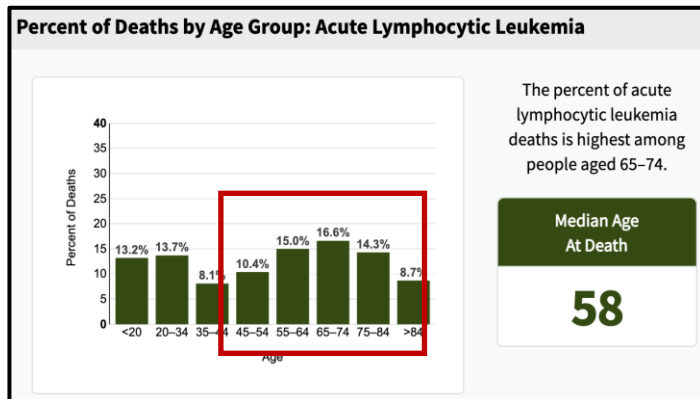
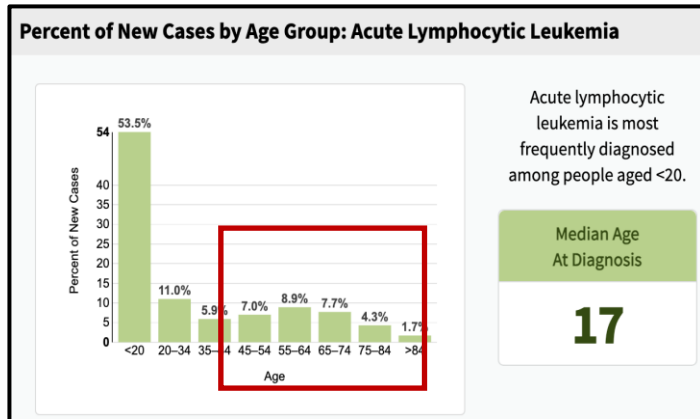
Survival (%)

Years since Diagnosis

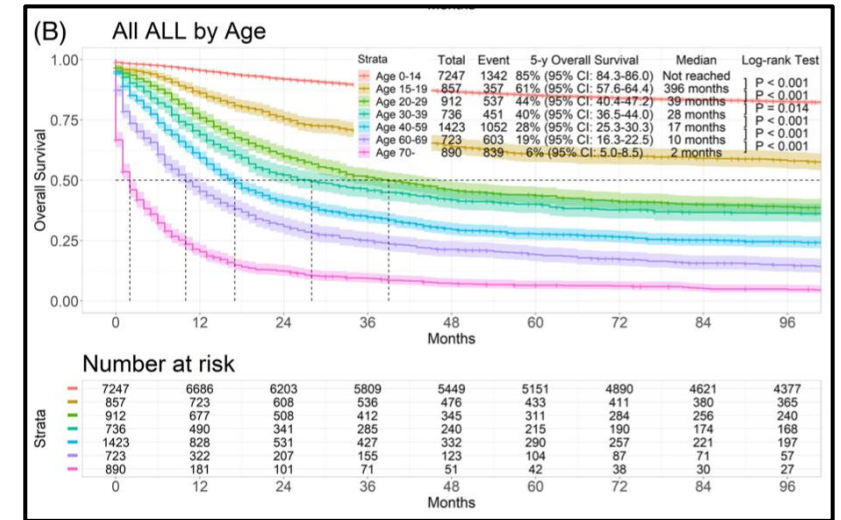
- **2025:** 75 years later, most children cured.
- How? Intensive, multi-agent, asparaginase-based, chemotherapy regimens, developed cooperatively and iteratively (with risk-based intensification)

CCG and COG trials, 1968-2009

ALL – In adults, more work to be done



ECOG 2003



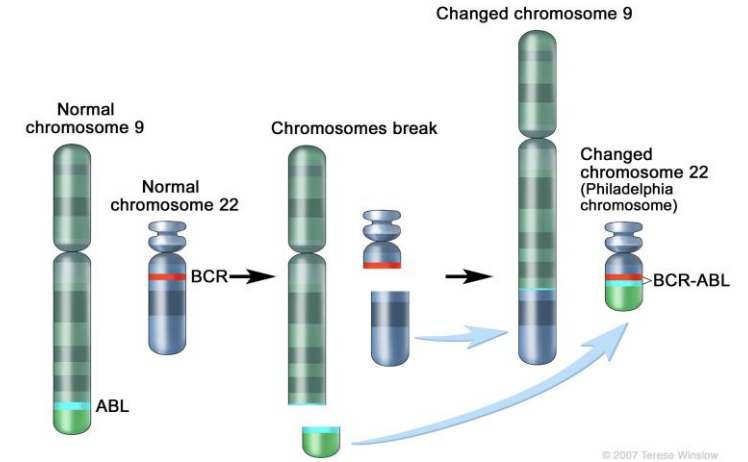
SEER Analysis 1980-2017

- Outcomes worsen with increasing age
- Particularly impacting older adults
- Higher risk ALL plus poor tolerability of chemotherapy

ALL – Framework for treatment

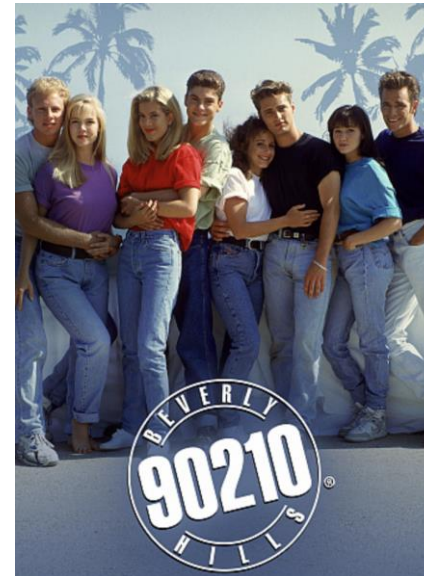
Therapeutic decisions guided by:

1) Philadelphia-chromosome status



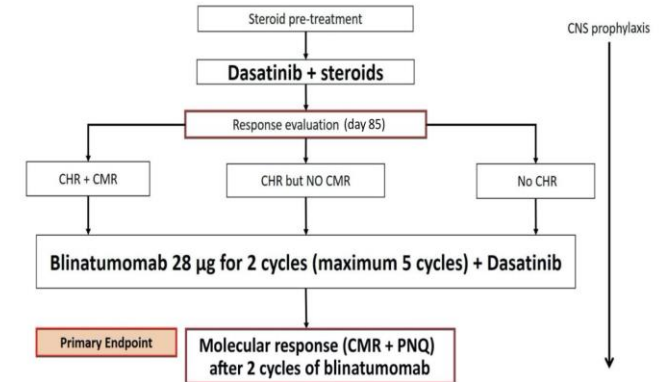
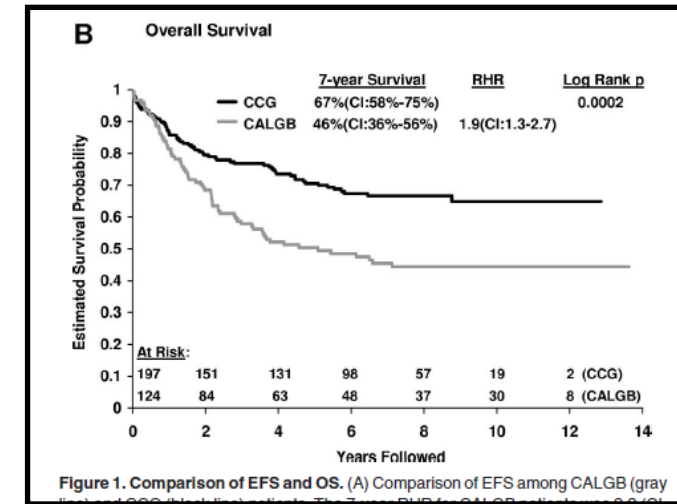
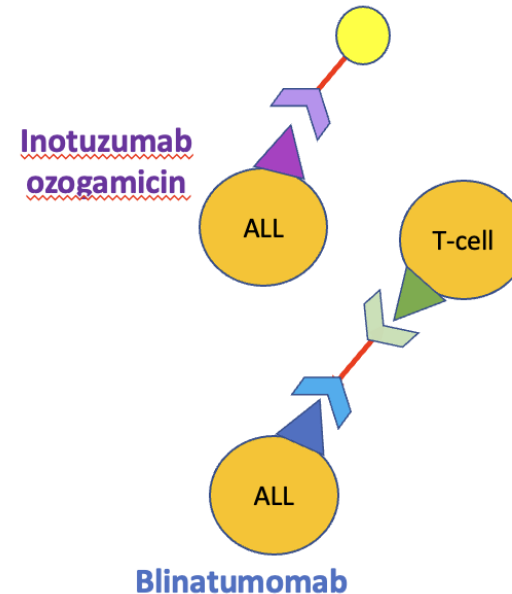
2) Age/fitness for chemotherapy

- AYA: Pediatric-inspired
- Adult: Standard intensity
- Older/comorbidities: Less intense, *novel agents*



ALL – Improvements accruing in adults

- **For young adults**, intensive, pediatric-inspired regimens (asparaginase-based)
- **For everyone**, novel immunotherapy (blinatumomab, inotuzumab ozogamicin) replacing conventional chemotherapy in induction and consolidation
- **For Ph+ ALL**, TKIs and blinatumomab



Acute leukemia conclusions

- **Acute leukemias are aggressive cancers of immature cells (“blasts”)**
 - Develop over a short time frame
 - Diagnosis made by confirming blasts, and determining lineage
 - Myeloid or lymphoid
 - Acute promyelocytic leukemia (APL) is a unique AML subtype characterized by early mortality due to coagulopathy, early recognition is critical
- **Treatment is focused on achieving remission (CR), and maintaining remission**
 - Treatment tailored to leukemia subtype, disease risk (predicted sensitivity to treatment), and patient age and comorbidities.
 - Some patients may be cured
- **Patients with acute leukemia need excellent internal medicine** – recognition and co-management!

Myelodysplastic syndromes (MDS)

Group of chronic, myeloid-lineage hematologic neoplasms characterized by **ineffective, clonal hematopoiesis**

Diagnosis: Bone marrow biopsy

- 1) Cytopenias (Hg <13/12 g/dL, plts <150 K/uL, ANC <1.8 K/uL)
- 2) MDS-defining abnormality:
 - Dysplasia ($\geq 10\%$ in 1 or more lineage)
 - Defining genetic abnormality
 - Blasts: BM ($\geq 5\%$ - <20%); blood ($\geq 2\%$ - <20%)

If ONLY dysplasia, make sure to rule out secondary causes of pancytopenia as other etiologies (medications, illness, age) can cause dysplasia

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 <i>SF3B1</i> mutation ^a (MDS- <i>SF3B1</i>)		Absence of 5q deletion, monosomy 7, or complex karyotype	<i>SF3B1</i>
MDS with biallelic <i>TP53</i> inactivation (MDS-bi <i>TP53</i>)	<20% BM and PB	Usually complex	Two or more <i>TP53</i> mutations, or 1 mutation with evidence of <i>TP53</i> 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		

^aDetection of $\geq 15\%$ ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.

^bBy definition, $\leq 25\%$ bone marrow cellularity, age adjusted.

BM bone marrow, PB peripheral blood, cnLOH copy neutral loss of heterozygosity.

I de-emphasize path classification in patient discussions, and focus on risk stratification.

What is MDS? (the ABCs)

- **Hallmarks of the disease (“the ABCs”):**
 - Risk of progression to **A**ML
 - **B**one marrow failure (progressive cytopenias)
 - **C**lonality indicates **c**ancer (almost all have abnormal karyotype and/or at least one molecular gene mutation)
- *Molecular mutations*: May help confirm, or be supportive of diagnosis but typically need other supporting features (not specific or sufficient)
- Widely varied presentation and risk of progression
- Some patients are asymptomatic, others experience substantial symptom burden

	'Non-clonal' ICUS	CHIP	CCUS	Lower Risk MDS	Higher Risk MDS
Clonality	–	+	+	+	+
Dysplasia	–	–	–	+	+
Cytopenias	+	–	+	+	+
BM Blast %	< 5%	< 5%	< 5%	< 5%	< 19%
Overall Risk	Very Low	Very Low	Low (?)	Low	High
Treatments	Obs/BSC	Observation	Obs/BSC/GF	Obs/BSC/GF IMiD/IST	HMA/HCST



Clonal Cytopenias

MDS – Clinical presentation

Symptoms: Mostly asymptomatic or related to fatigue

- **Common:** None, fatigue, weakness, angina, dizziness, cognitive impairment
- **Less common:** Infection, easy bruising, bleeding, fever, weight loss

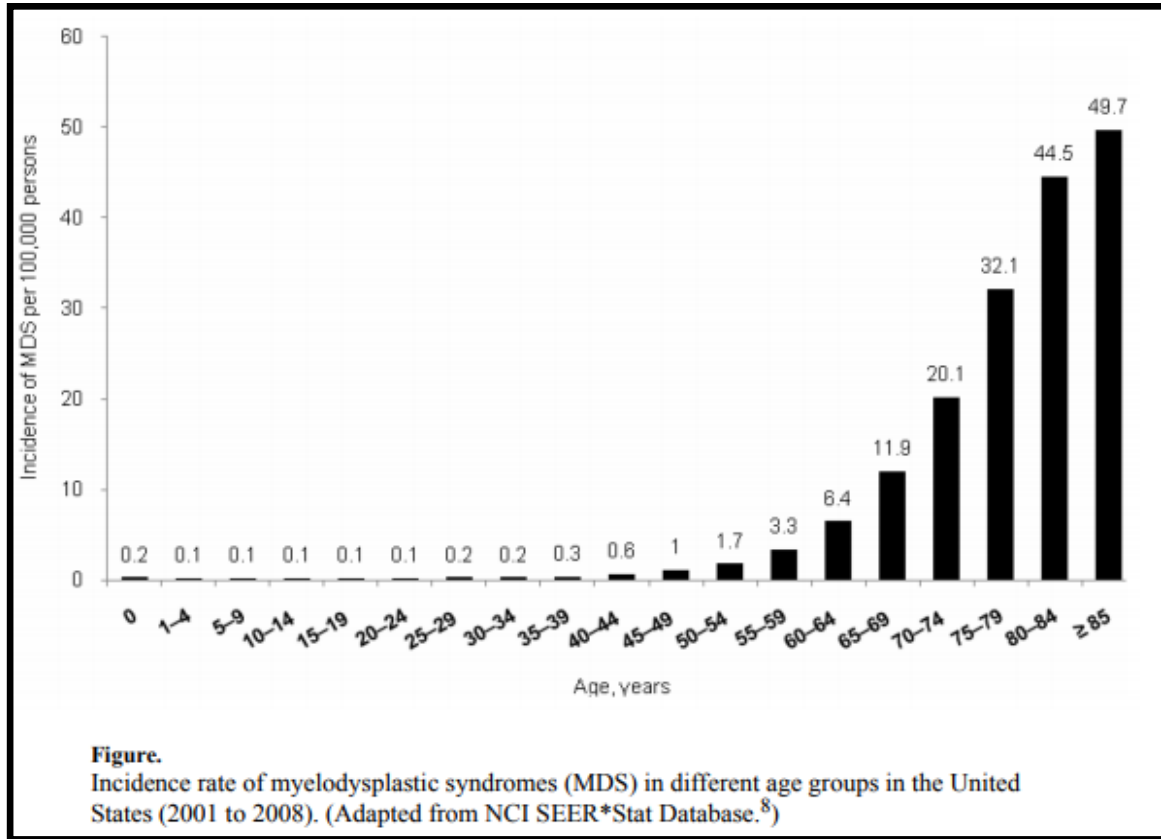
Lab: Cytopenias (and abnormal peripheral smear)

- **90% anemia** (usually macrocytic or normocytic, RDW may be increased)
- 50% leukopenia, 25% thrombocytopenia, 50% pancytopenia
- Isolated neutropenia and thrombocytopenia less common

Exam: Benign, or symptomatic anemia

- Pallor, petechiae, purpura
- *Hepatomegaly, splenomegaly, lymphadenopathy rare*
- Sweets syndrome (neutrophilic dermatosis)

MDS – Epidemiology



- Median age at diagnosis: ~70-75 years
- Approximately 40,000 cases/year
- Low blood counts in older adults often incompletely evaluated.
- *Risk factors:*
 - Typical: Age, male gender, clonal hematopoiesis, prior chemotherapy/radiation
 - Young onset: aplastic anemia, inherited predisposition syndromes

MDS – Risk scores

IPSS

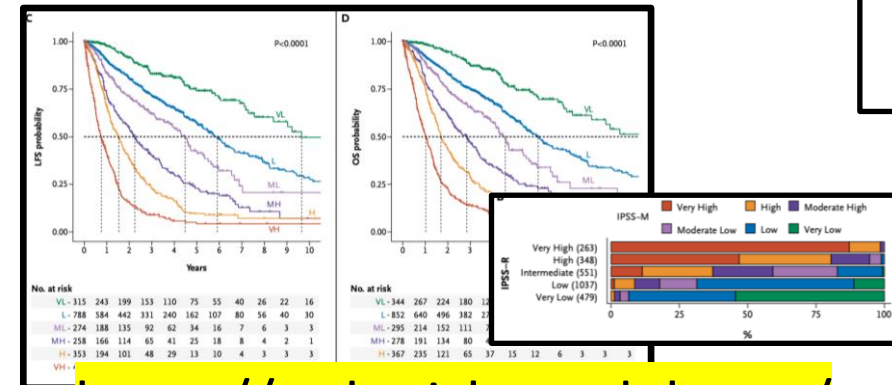
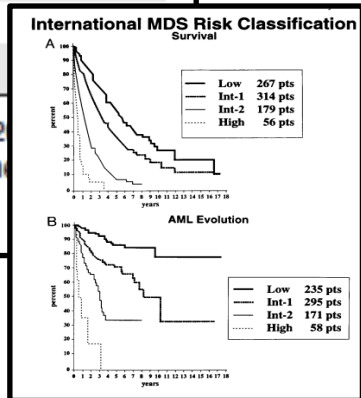


- Do not stage like solid tumor (i.e stage I-IV)
- **Goal to understand pace of disease worsening:**
 - Further bone marrow failure
 - Progression to AML
- **International Prognostic Scoring System (IPSS) /IPSS-Revised/IPSS-Molecular developed to estimate:**
 - Time to AML progression
 - Overall survival
- **Integrate disease features associated with risk:**
 - Number and degree of cytopenias
 - Presence and degree of excess blasts
 - Genetics (karyotype and molecular - NGS)

Table 1. International Prognostic Scoring System (IPSS): prognostic variables

	0	0.5	1.0	1.5	2.0
Marrow blasts, %	<5	5-10	—	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3	—	—	

— indicates not applicable; Good = normal, -y, del(5q), del(2 complex (≥3 abnormalities) or chromosome 7 anomalies; and Intermediate other abnormalities.



<https://mds-risk-model.com/>



MDS – Treatment

Supportive care

- Goal: Improve quality of life
- Who: Any with symptoms

Define goals of therapy

- 1) Symptom control
- 2) Lengthen life
- 3) Cure

Disease modifying treatment

- Goal: Lengthen life, ?cure
- Who: High-risk disease.

- Transfusions
- Erythropoietin, TPO mimetics
- Lenalidomide (esp: *del5q*)
- Low risk/anemia: Luspatercept (TGFB trap), imetelstat (telomerase inhibitor).
- Immune suppression (*consider for hypoplastic MDS*)



Ongoing reassessment, education, and counseling!

- Azacitidine and decitabine (chemotherapy)
- Curative: Allogeneic stem cell transplant

Hypomethylating agent chemotherapy

Azacitidine, decitabine

- Improvement in OS and delayed progression to AML in high-risk patients
- May be used to treat cytopenias when other drugs failed:
 - Few complete remissions (<20%) but ~50% have some hematologic improvement

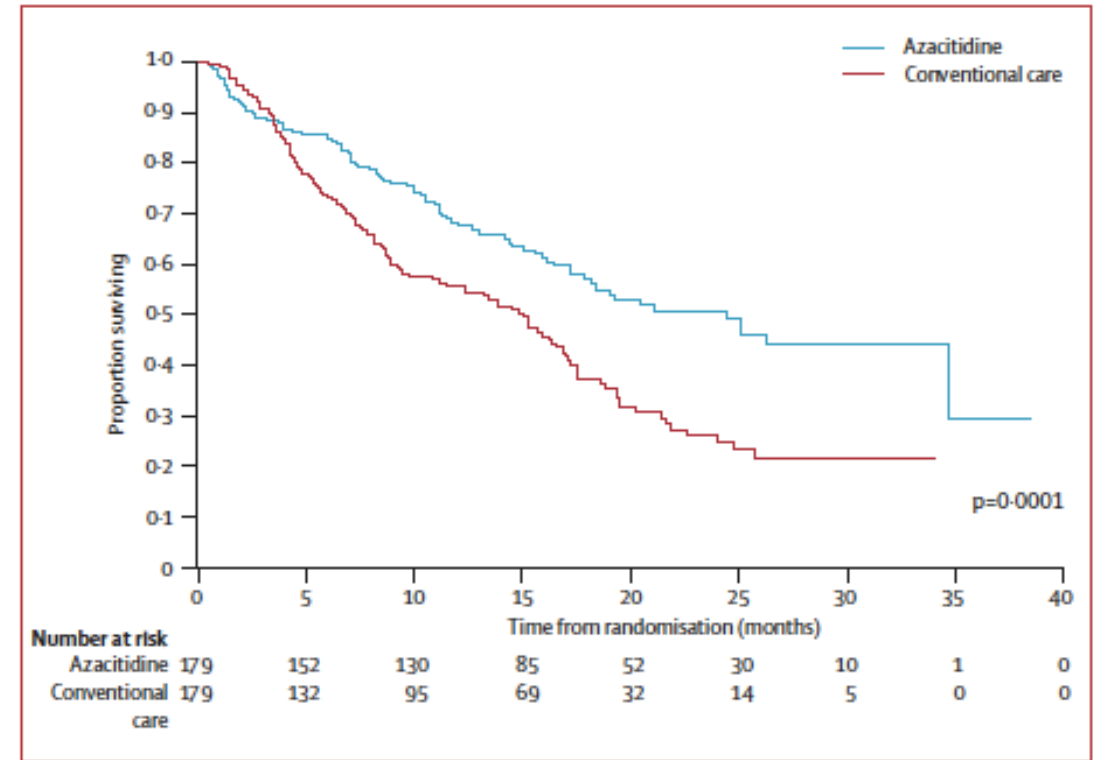
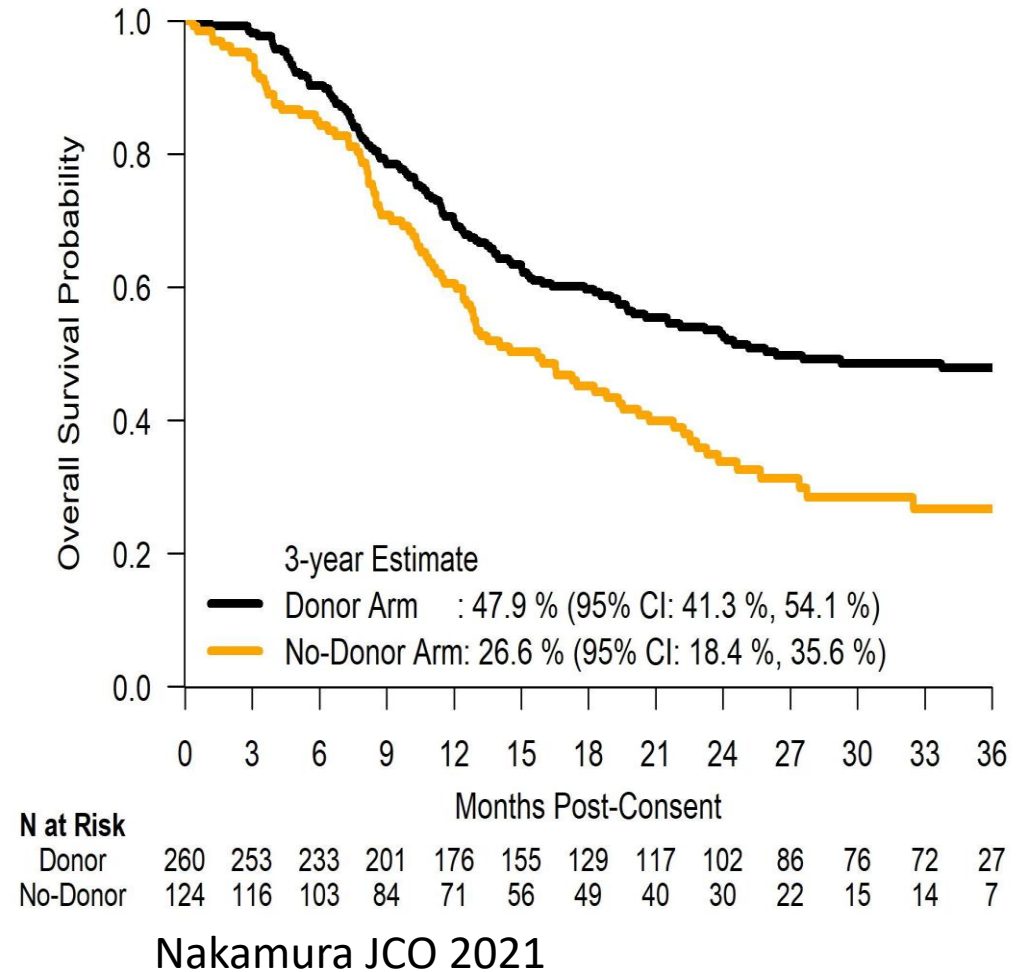


Figure 3: Overall survival

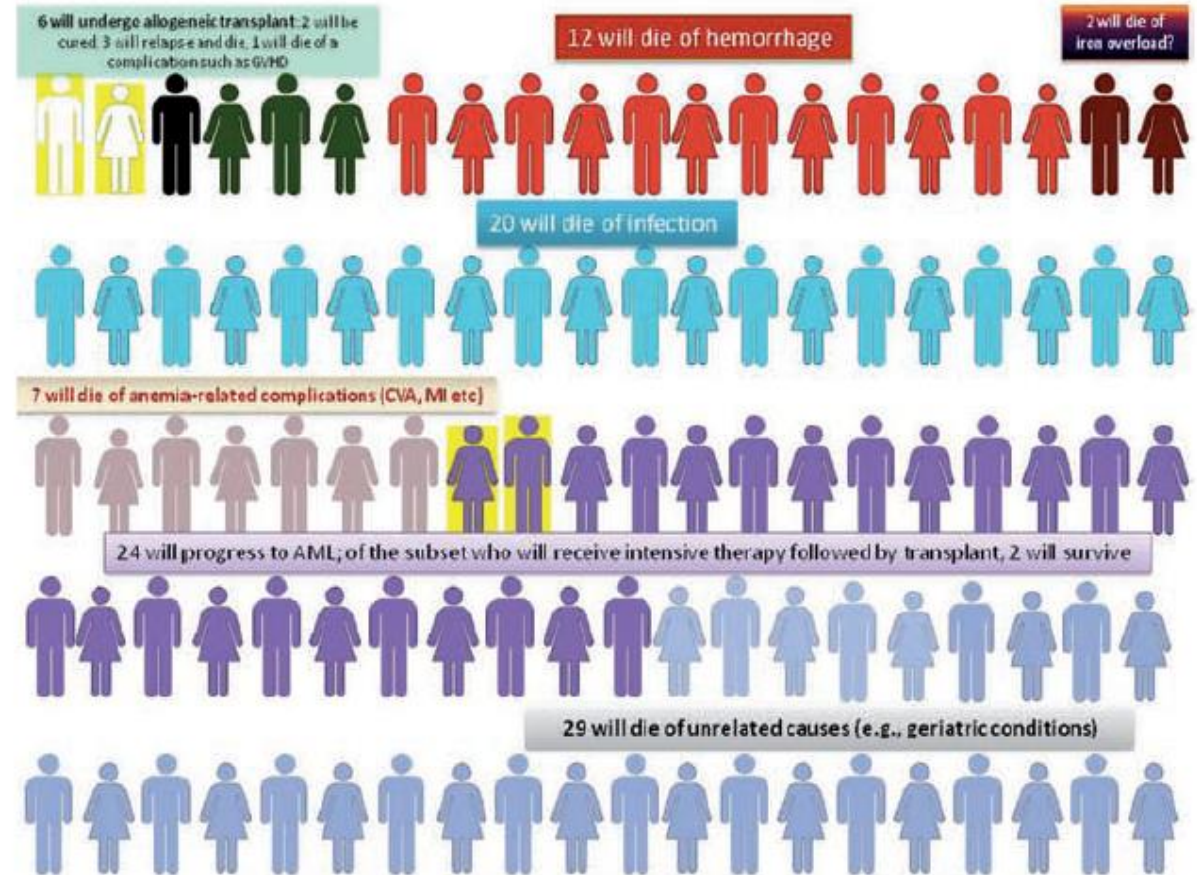
Transplant for MDS

- Only curative therapy.
- Indicated for **IPSS Int-2/High**
 - Retrospective (Markov models) – Cutler, Koreth
 - Prospective BMTCN 1102 Trial (aged 50-75 years, IPSS Int-2 or High)
- *If fit*, age is not an exclusion until ~80 years old!

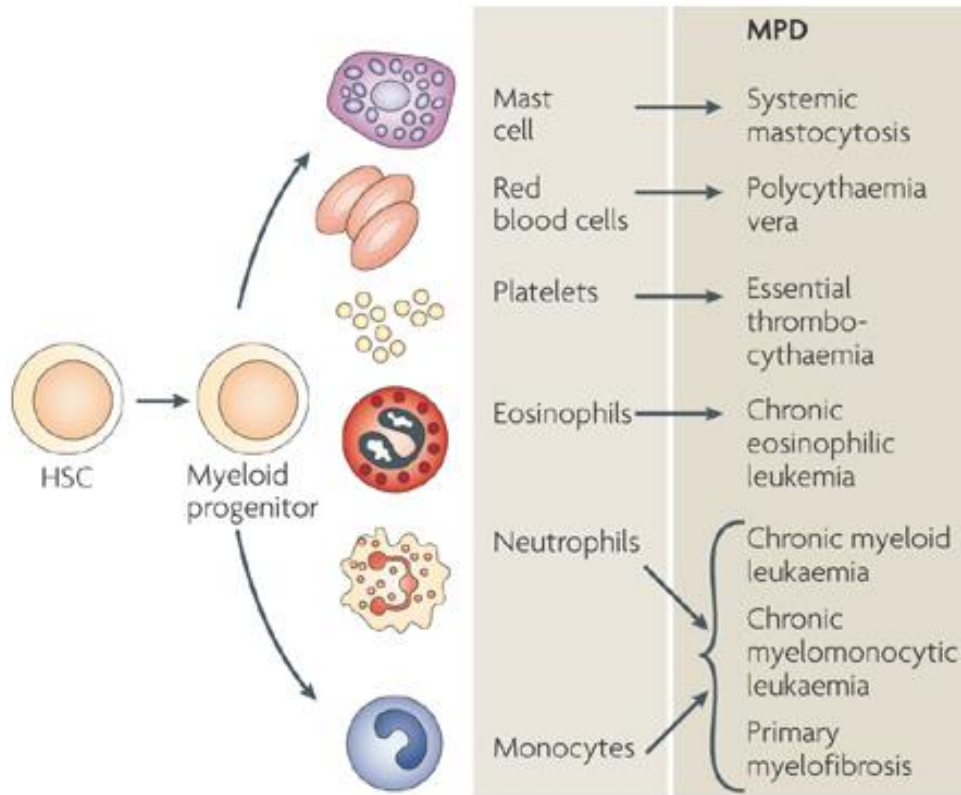


MDS – Death

- **Acute myeloid leukemia**
- **Progressive cytopenias** (can be just as bad as “acute” transformation” in terms of impact on patient)
 - Cardiovascular
 - Bleeding
 - Infection
- **Complications of treatment**
- **Unrelated causes** (die with disease)



Myeloproliferative neoplasms (MPNs) → overproduction of myeloid lineage cells



KIT D816V

JAK2 V617F or Exon 12

JAK2 V617F, MPL, CALR

FIP1L1::PDGFRA

BCR::ABL1

TET2, ASXL1, SRSF2

JAK2 V617F, MPL, CALR

Chronic myeloid leukemia (CML)

- **Myeloproliferative neoplasm (MPN)**
 - Over-production of myeloid-lineage cells
 - No differentiation arrest or dysplasia
- **Peripheral blood:** Leukocytosis
 - Neutrophil predominant
 - Full spectrum granulocytic series
 - Clues: “myelocyte bulge,” eosinophilia and basophilia
- **Bone Marrow:** Hypercellular, granulocytic (myeloid) hyperplasia, elevated M:E ratio, small megakaryocytes with hypo-lobated nuclei (“dwarf megakaryocytes”)

Table 1. WHO classification of myeloid neoplasms and acute leukemia

WHO myeloid neoplasm and acute leukemia classification

Myeloproliferative neoplasms (MPN)

Chronic myeloid leukemia (CML), *BCR-ABL1*⁺

Chronic neutrophilic leukemia (CNL)

Polycythemia vera (PV)

Primary myelofibrosis (PMF)

PMF, prefibrotic/early stage

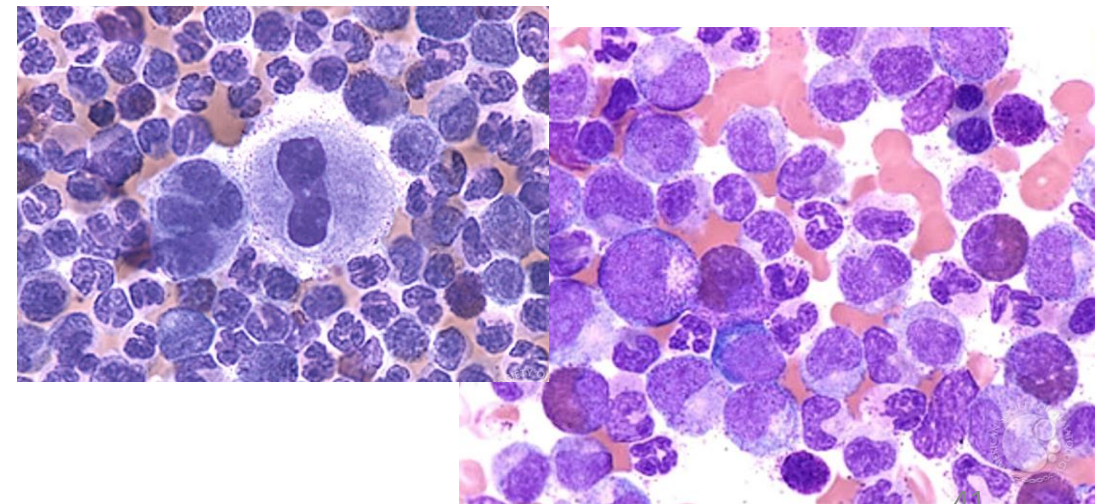
PMF, overt fibrotic stage

Essential thrombocythemia (ET)

Chronic eosinophilic leukemia, not otherwise specified (NOS)

MPN, unclassifiable

**Defined by the Philadelphia chromosome
(*BCR::ABL1* translocation)**



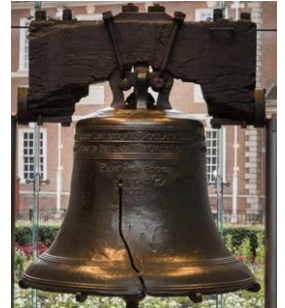
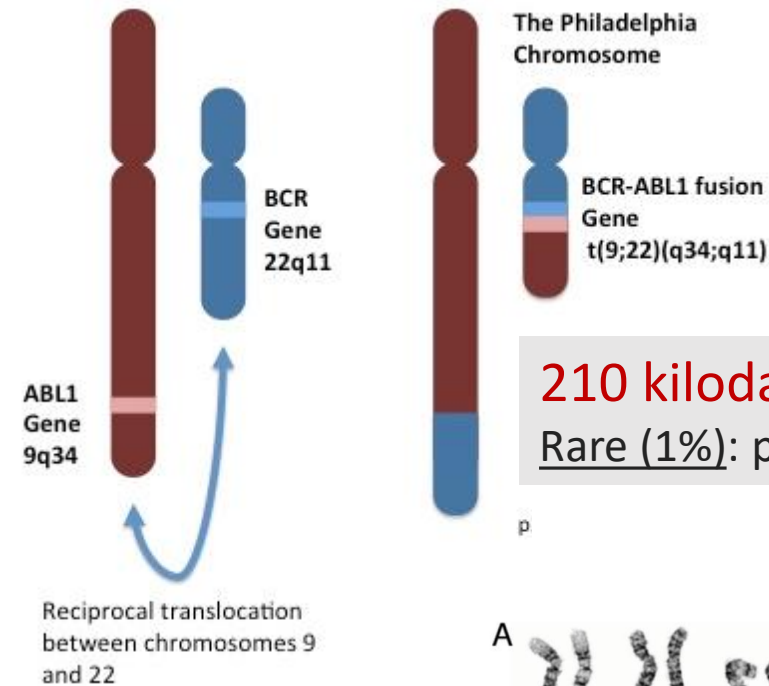
CML is defined by the Philadelphia chromosome

Philadelphia chromosome = $t(9;22)$ = *BCR::ABL1* fusion

Constitutively active ABL1 tyrosine kinase due to fusion with BCR

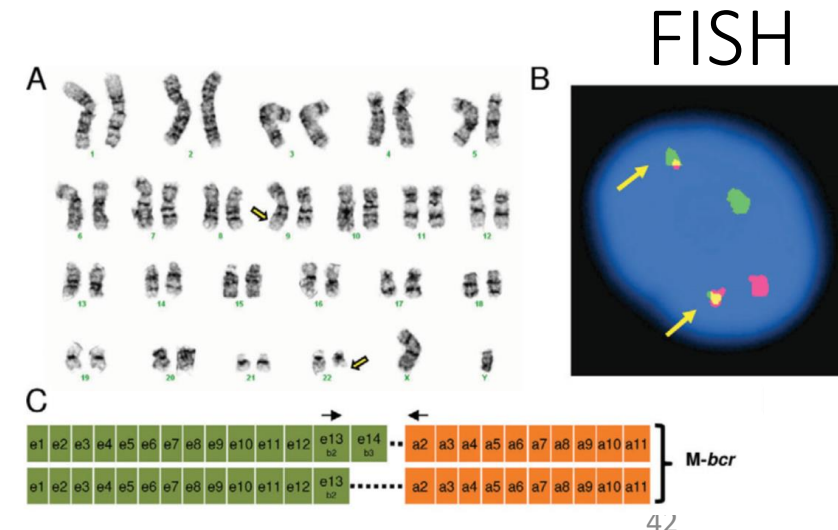
Uncontrolled granulocytic proliferation

Note: $t(9;22)$ also seen in ALL (usually p190 but ~1/3 p210), and rarely AML



210 kilodalton (B3A2 or B2A2)
Rare (1%): p190 (e1a1), p230 (e19a2)

Karyotype



CML – Diagnosis

For treatment planning, need careful assessment of medications, and comorbidities, especially pulmonary, cardiovascular and diabetes.

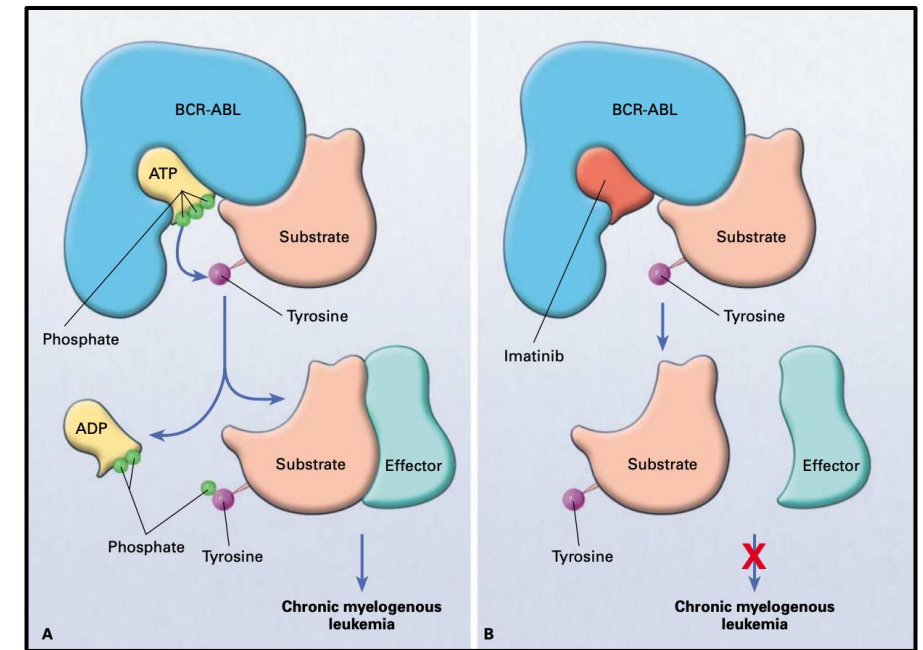
- **Clinical: non-specific**
 - Asymptomatic (incidental lab finding)
 - Symptoms: Fatigue, malaise, weight loss, symptomatic splenomegaly (abdominal fullness, pain, anorexia), gout
- **Suspicion:** Characteristic blood counts and bone marrow pathology
- **Confirm:** t(9;22)(q34.1;q11.2)/*BCR::AB/1* fusion by cytogenetics, FISH, or RT-PCR

Pearl: Send *BCR::ABL1* p210 RT-PCR for all unexplained (non-lymphoid) leukocytosis This is a DO NOT MISS diagnosis given excellent treatment options

Pearl: A bone marrow biopsy is necessary for staging

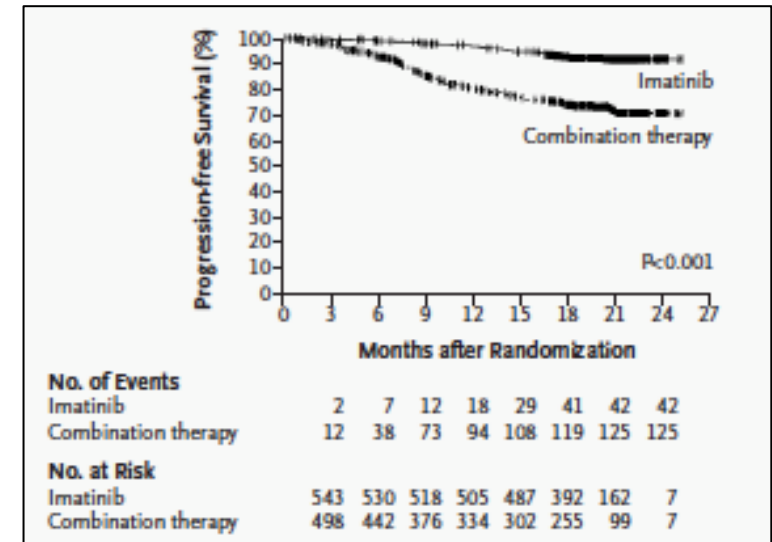
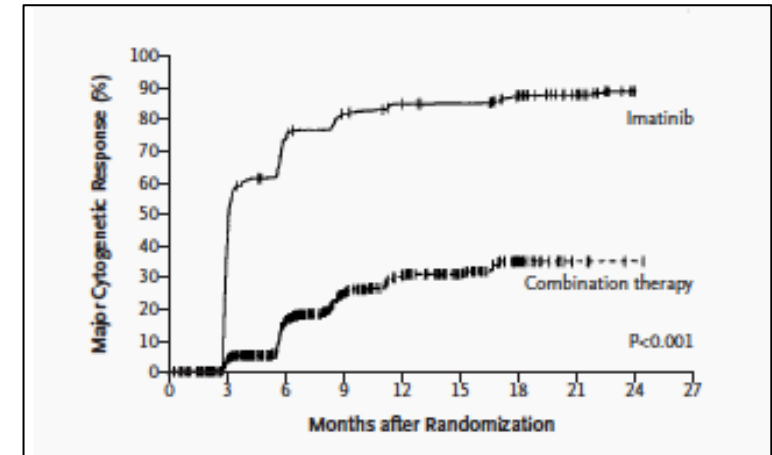
CML – Treatment

- Alleviate disease related symptoms
- Prevent transformation to more aggressive forms of CML (accelerated or blast phase) which are markedly more difficult to treat
- TKIs are primary modality of therapy
 - **Imatinib** – first BCR::ABL1 tyrosine kinase inhibitor (TKI) - transformed treatment prognosis of CML
 - **Now** – 6 approved TKIs for CML, 5 for initial treatment



IRIS – Imatinib transforms CML treatment

- Imatinib was the first TKI for CML
- The IRIS trial randomized patients with CML in CP to imatinib versus cytarabine and interferon
- Imatinib patients had dramatically higher rates of achieving cytogenetic remission
- Less likely to experience progression to advanced phase disease



Druker et al. *Nat Med* 1996;2:561; O'Brien et al. *N Engl J Med* 2003;348:994;
 Druker et al. *N Eng J Med* 2006;355:2409

Event = AP disease, BC disease, lost of hematologic remission, loss of major cytogenetic response

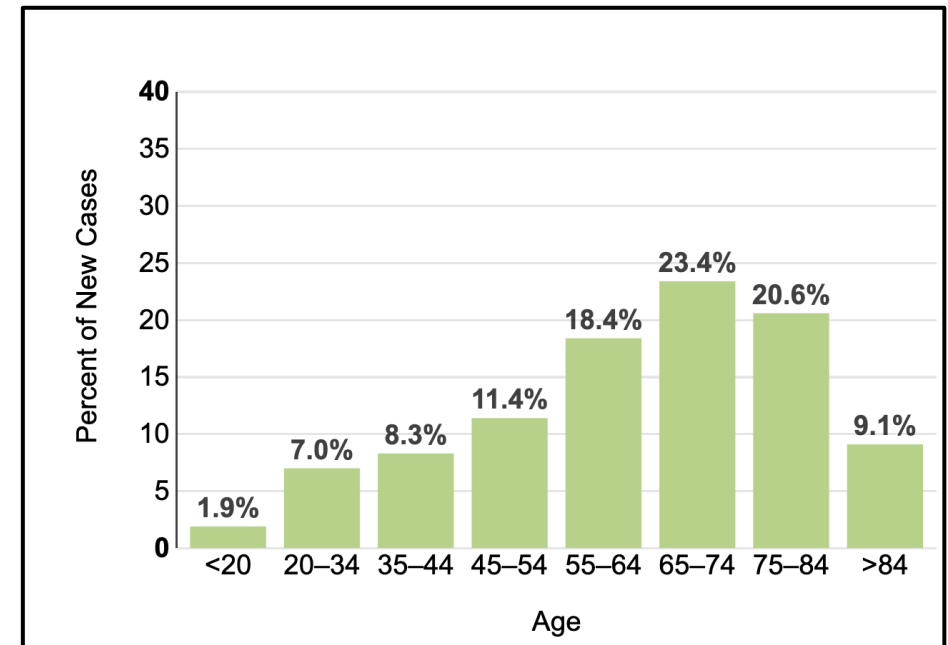
CML – Epidemiology

- **New cases in 2025: 9,560**
 - 0.5% of new cancer cases, ~15% of adult leukemias.
 - Lifetime risk: 0.2%, M=F
- Dramatic improvements in survival are leading to increased prevalence
- **Pearl: We will all see more of this disease!**
- **In 2022, estimated 74,198 people living with CML in the US**

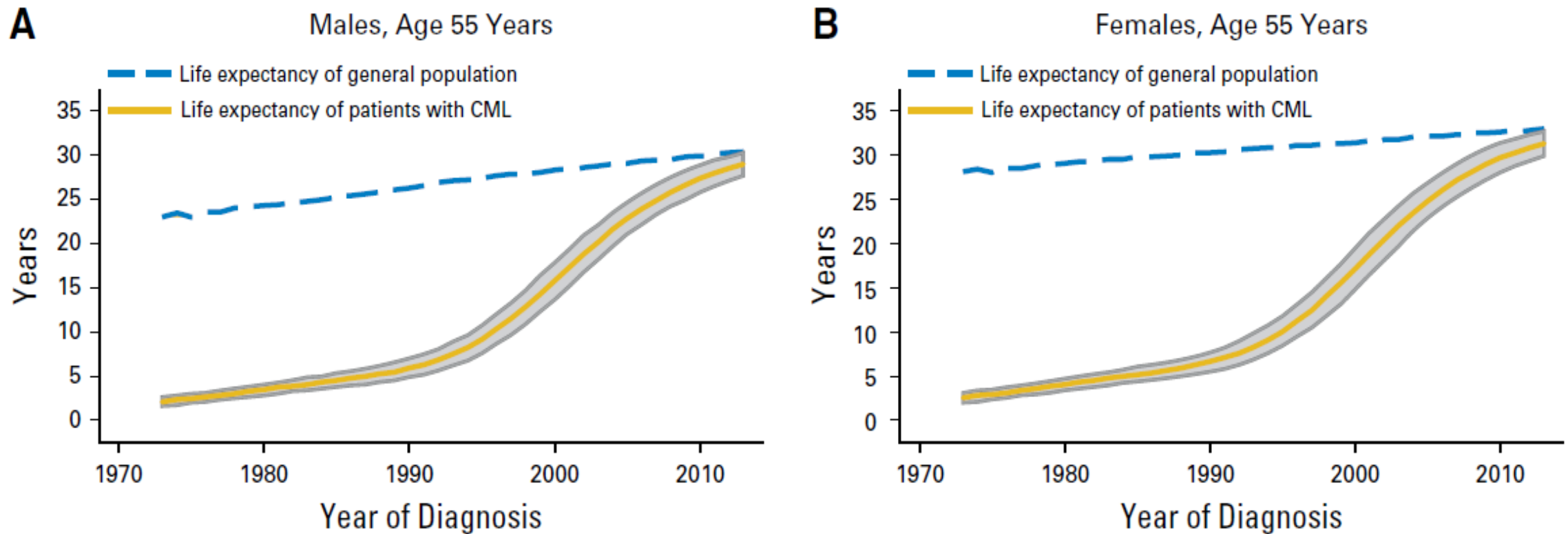
Chronic myeloid leukemia is most frequently diagnosed among people aged 65–74.

Median Age
At Diagnosis

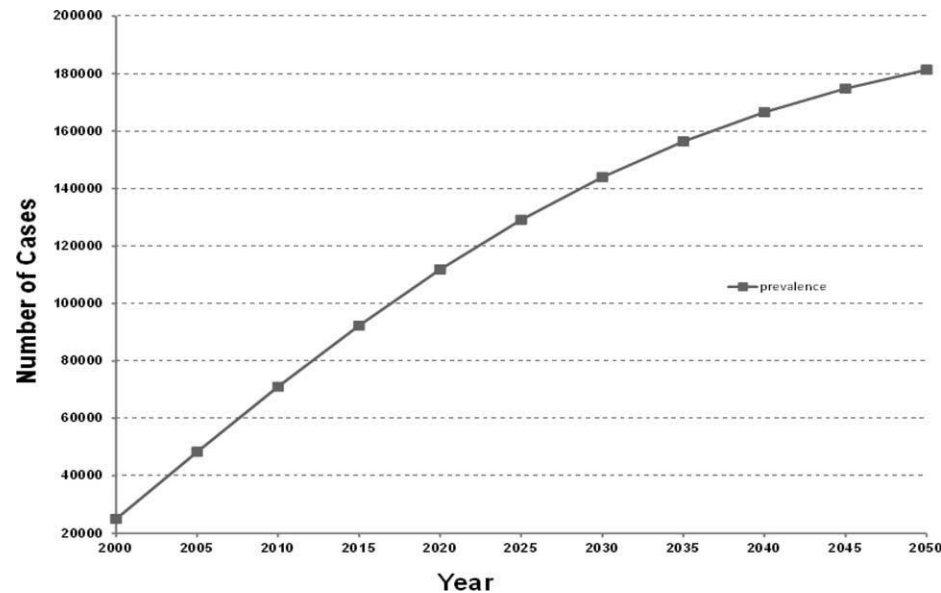
66



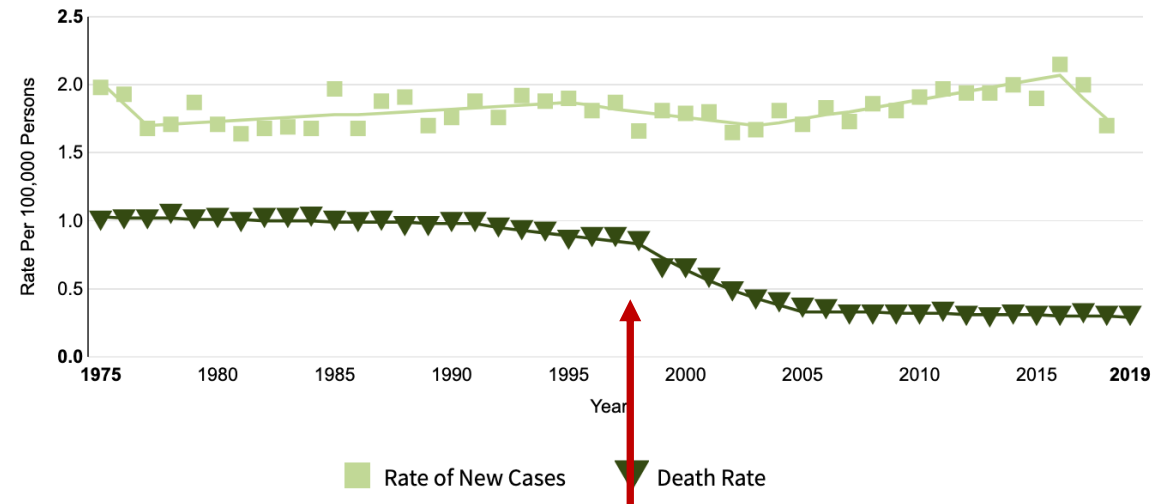
CML – Life expectancy approaching age matched population



CML – Increased prevalence



“The prevalence of CML will continue to increase to reach a near plateau prevalence 35 times the annual incidence.”



Imatinib

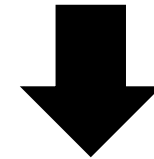
CML treatment overview – 2026

Imatinib
Nilotinib
Dasatinib
Bosutinib
Asciminib



Refractory
Suboptimal response
Relapse
Intolerance

Imatinib
Nilotinib
Dasatinib
Bosutinib
Asciminib
Ponatinib



Allogeneic HSCT (Rare)

ATP Binding Site

- **1st generation:** Imatinib
- **2nd generation:** Nilotinib, dasatinib, bosutinib
 - More potent, active against resistance mutations
- **3rd generation:** Ponatinib
 - Most potent, active against *T315I*

Allosteric inhibitor: Asciminib

- Very potent, active against *T315I* (need higher dose), well-tolerated

TKIs – Toxicity

Later generation TKIs –

- 1) Faster, deeper remissions, no survival benefit
- 2) Have (or may have) more toxicity

Imatinib (daily w food)	Fluid retention, peri-orbital edema, GI upset (diarrhea, nausea), rash, myalgias, low phosphorus – <i>long-term follow-up confirms no late CV/pulm tox</i> ,
Dasatinib (daily w or w/o food)	Pleural effusions (~20%), pulmonary hypertension (rare, but serious), gastrointestinal bleeding/platelet dysfunction, lymphocytosis/adenopathy
Nilotinib (twice daily w/o food)	Peripheral arterial occlusive disease, hyperglycemia, hyperlipidemia, QT prolongation, transaminitis/hyperbilirubinemia, elevated amylase/lipase, elevated bilirubin. Least hematologic toxicity.
Bosutinib (daily w food)	Transaminitis, diarrhea (<i>LESS with improved management</i>). No cardiovascular signal.
Asciminib (once or twice daily w/o food)	Increase in amylase/lipase (?clinical pancreatitis), hypertension, short follow-up .

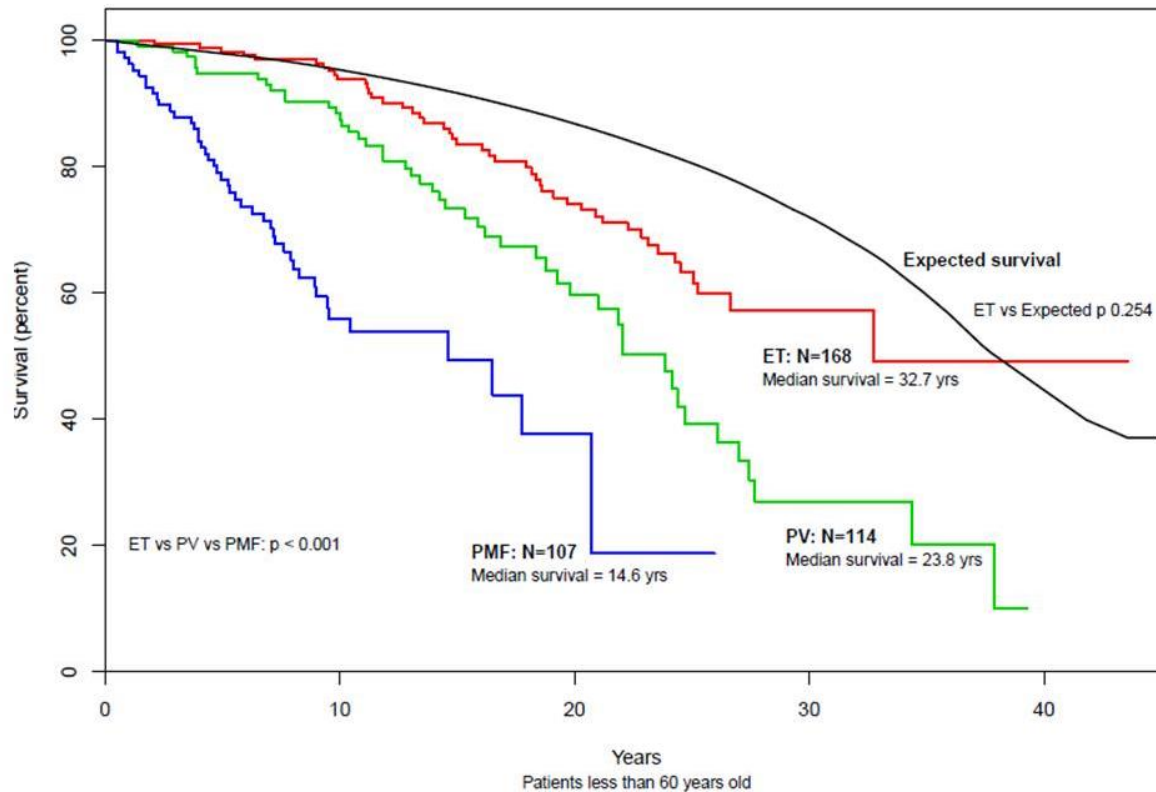
Pearl: Imatinib increases serum creatinine by inhibiting tubular secretion (reversible).

Pearl: Adenopathy in a dasatinib treated patient may be related to drug.

Pearl: Arterio-occlusive events occur LATE, likely accrued after closure of many trials.

Moslehi et al. *J Clin Oncol* 2015;33:4210; Kalmanti et al. *Leukemia* 2015;29:1123; Steegman et al. *Leukemia* 2016;30:1648; Vidal-Petiot et al. *Clin Lymphoma Myeloma Leuk* 2016;169; Veltmatt and Cortes et al *Blood* 2024;143:858

Ph-negative MPNs



- Generally indolent clinical course.
- ET and PV can progress to fibrotic stage (post-ET or post-PV MF)
- All MPNs can progress to accelerated/acute phase disease (with increase in blasts) – i.e. acute myeloid leukemia.

Ph-negative MPNs – treatment approach

- **“Low-risk” patients** – long survival without need for major intervention
 - If symptomatic – supportive treatments employed
 - Various risk scores available for different diseases (DIPSS for PMF, CPSS-Mol for CMML, IPSET for ET, etc.)
- **Risk of thrombosis** – especially ET and PV, *with JAK2 V617F*
 - Aspirin
 - Phlebotomy for patients with PV and HCT >45%
 - Cytoreduction: Hydroxyurea, (or ropeginterferon, or ruxolitinib) for “high risk” patients (age >60 years, history of thrombosis)
 - Control of cardiovascular risk factors
- **High risk patients/accelerated phase disease**
 - Chemotherapy, allogeneic transplant

MDS/MPN overlap syndromes

- **Diseases with features of BOTH**
 - Myelodysplastic syndrome
 - Cytopenias
 - Dysplasia
 - Myeloproliferative neoplasm
 - Cytosis
 - Splenomegaly
- **Most common example is chronic myelomonocytic leukemia (CMML)**
 - Cytopenias and dysplasia common
 - Monocytosis and splenomegaly common
- **Management extrapolated from treatment of MDS and MPNs**

Non-acute leukemia conclusions

- **Non-acute myeloid leukemias are less aggressive myeloid neoplasms with no or less severe differentiation impairment (no or only mild increased in blasts)**
 - Develop over longer time frame
 - Diagnoses categorized as dysplastic (MDS), proliferative (MPNs), or overlap
 - MDS – dysplasia, cytopenias
 - MPN – proliferation of one or more cell lineage
 - Ph+ MPN (CML) – presence of t(9;22)
- **Treatment is based on symptoms and risk**
 - In all, manage symptomatic cytopenia or cytolysis if present. In Ph- MPNs, aspirin and cytoreduction to reduce risk of thrombosis.
 - In high-risk patients implement treatment to modify natural history (chemotherapy, transplant)
 - CML is treated with TKIs to prevent disease progression.

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- O'Brien et al. *N Engl J Med* 2003;348:994-1004 **Benefit of imatinib in CML**
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Find a field of medicine you love, a patient population you love caring for, and a team you love being a part of!

Question 1

A 54-year-old male presents with WBC 230,000/uL. He denies bruising, bleeding. He has a large spleen. Hemoglobin and platelets are normal. Bone marrow biopsy demonstrates chronic myeloid leukemia. What is the hallmark chromosomal finding of this?

- a. MLL (11q23) rearrangement
- b. 9;22 translocation (Philadelphia chromosome)
- c. 15;17 translocation
- d. Loss of chromosome 7

Question 1 Answer

A 54-year-old male presents with WBC 230,000 K/uL. He denies bruising, bleeding. He has a large spleen. Hgb and Platelets are normal. Bone marrow biopsy demonstrates chronic myeloid leukemia. What is the hallmark chromosomal finding of this?

- a. MLL (11q23) rearrangement
- b. 9;22 translocation (Philadelphia chromosome)
- c. 15;17 translocation
- d. Loss of chromosome 7

Chronic Myeloid Leukemia is DEFINED by the presence of the Philadelphia chromosome and is required for diagnosis

Question 2

A 26-year-old female presents after 2 ER visits for vaginal bleeding, not improved. CBC shows pancytopenia. Fibrinogen is 60, INR is 1.9. She is found to immature cells on her smear with Auer rods. What is her most likely diagnosis?

- a. Acute lymphoblastic leukemia
- b. Chronic myeloid leukemia
- c. Myelodysplastic syndrome
- d. Acute promyelocytic leukemia

Question 2 Answer

A 26-year-old female presents after 2 ER visits for vaginal bleeding, not improved. CBC shows pancytopenia. Fibrinogen is 60, INR is 1.9. She is found to immature cells on her smear with Auer rods. What is her most likely diagnosis?

- a. Acute lymphoblastic leukemia
- b. Chronic myeloid leukemia
- c. Myelodysplastic syndrome
- d. **Acute promyelocytic leukemia**

APL is characterized by younger age, circulating promyelocytes with granules and Auer rods, and coagulopathy. The diagnosis is confirmed by the presence of the t(15;17) translocation.