Leukemia for the Primary Care Physician (Non-CLL)

Karilyn Larkin, MD
Assistant Professor of Medicine
Division of Hematology
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

OBJECTIVES:

- Presenting symptoms
- Context and basic biology
- Diagnostics
- Prognostics
- Therapeutics

CASE 1

- Your longtime patient Mr. Smith, a 57-year-old man who works on his farm, presents with progressive fatigue and dyspnea on exertion over the last two weeks.
- He has shortness of breath with minimal activity and chest pain with climbing stairs, one month ago he was carrying 50lbs without any difficulty. He notes a headache that has been constant for the past day.
- He is able to sleep while laying flat on one pillow

CASE 1, CONTINUED

PMH:

HTN, HLD, Rheumatoid Arthritis

SH:

20pk/year smoking history, 1-2 drinks a few times a week, he lives on his farm with his wife and they have a large dog and 2 cats, 3 children whom are grown

FH:

CAD, prostate CA

Meds: lisinopril, simvastatin, methotrexate

CASE 1, CONTINUED

- Physical examination
  - Pale but not ill-appearing, with rapid heart rate; not short of breath at rest
  - Hypertrophied gums with areas of bleeding
  - No pitting edema, lungs are clear
  - No lymphadenopathy
  - +Ecchymoses on arms and legs

CASE 1, CONTINUED

- Complete blood count
  - WBC count: 55,000 cells/μL
  - Hemoglobin: 6 g/dL
  - Platelet count: 15,000 cells/μL
- CMP
  - Creatinine 1.5 (baseline 1.1), otherwise WNL
  - AST/ALT minimally elevated

WHAT DOES THE HEMATOLOGIST WANT TO KNOW?

- What are his coags? PT/PTT/INR AND Fibrinogen
- Uric Acid
- Has he had any fevers?
- Any headaches? Vision changes? Difficulty breathing or hypoxemia? Any chest pain?

WHAT ARE THE IMMEDIATE NEXT STEPS?

Report to the closest ER

(acute leukemia treating center if possible)

- These are the patients that keep me up all night

ACUTE LEUKEMIA PRESENTING SYMPTOMS

- Cytopenias
- Hyperleukocytosis → leukostasis
- Extramedullary disease
- Tumor lysis syndrome
- Disseminated Intravascular Coagulation

CASE 2

- Your longtime patient Mr. Habib, a 57-year-old man who works on his farm, presents with progressive fatigue and early satiety over the past several months.
- He denies any shortness of breath with minimal activity but notes some discomfort with deep inspiration and frequent sharp pains on his left side.
- He has been sleeping well and doesn't understand why he's feeling so fatigued

CASE 2, CONTINUED

- PMH: HTN, HLD
- SH: 20pk/year smoking history, 1-2 drinks a few times a week, he lives on his farm with his wife and they have a small dog and 2 hamsters, 2 children whom are grown
- FH:CAD, prostate CA
- Meds: lisinopril, simvastatin

CASE 2, CONTINUED

- Physical examination
  - Appears well, non-toxic, normal vitals
  - Cardiac exam unremarkable
  - No pitting edema, lungs are clear
  - No lymphadenopathy, but spleen is palpable 4 cm below left costal margin
  - No rashes or bruises

CASE 2, CONTINUED

- Complete blood count
  - WBC count: 55,000 cells/μL
  - Hemoglobin: 10 g/dL
  - Platelet count: 325,000 cells/μL
- CMP
  - Creatinine 1.2 (baseline 1.1), otherwise WNL
  - AST/ALT normal

WHAT DOES THE HEMATOLOGIST WANT TO KNOW?

- What does his PB smear look like?
- Uric acid
- When was his last CBC and what did it look like?

WHAT ARE THE IMMEDIATE NEXT STEPS?

Look at PB smear

↓

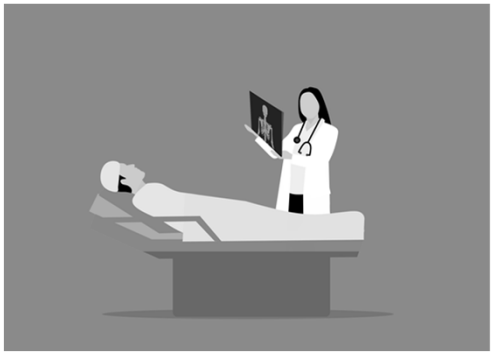
Send BCR/ABL

↓

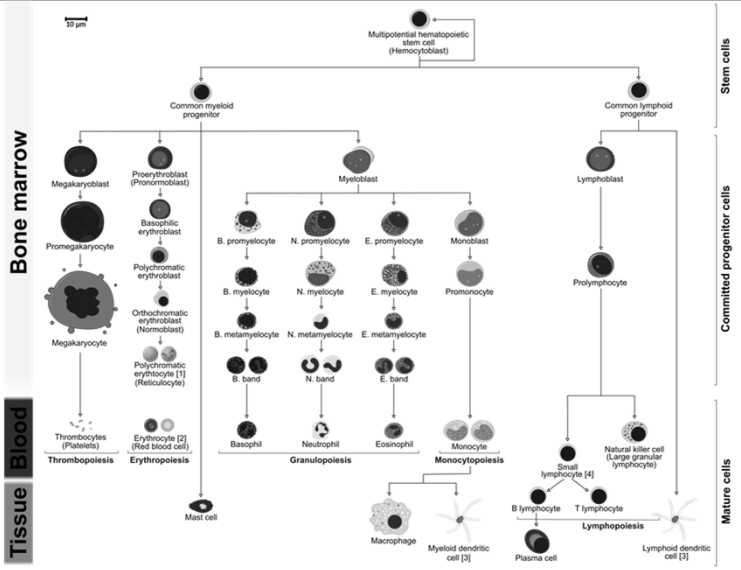
Can follow up in clinic

CML PRESENTING SYMPTOMS

- Mild Anemia, thrombocytosis
- Hyperleukocytosis
- Splenomegaly, +/- infarcts
- Hyperuricemia



WHAT IS LEUKEMIA?



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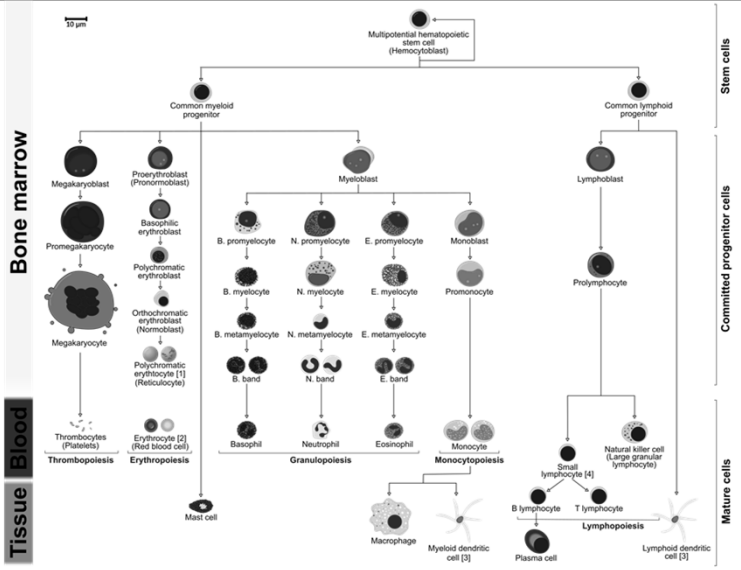

Acute

Chronic

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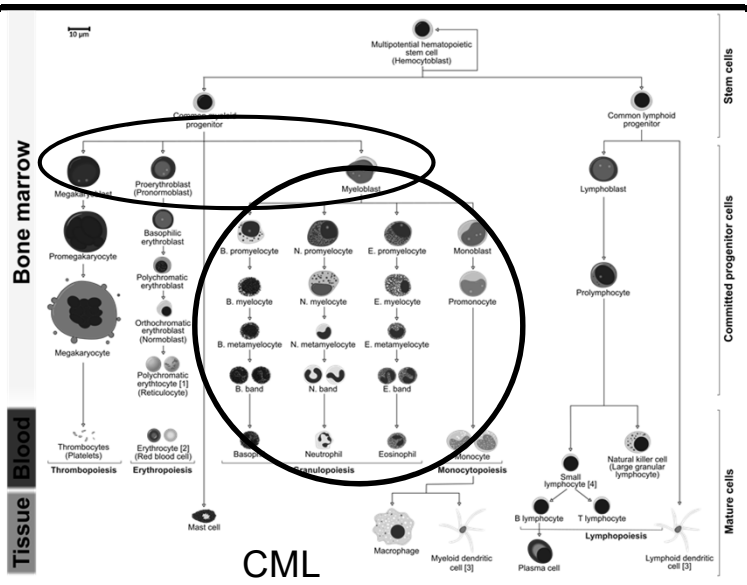
WHAT IS LEUKEMIA?

AML



CML

Image courtesy of wikipedia
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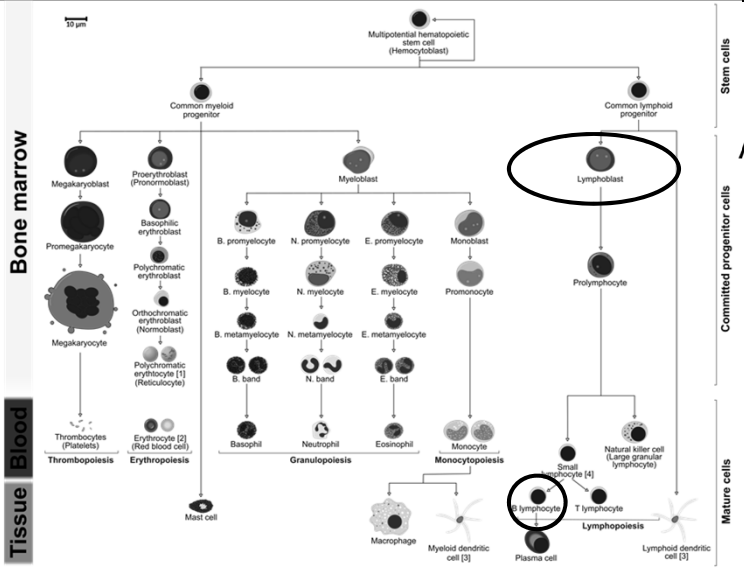

ALL

CLL

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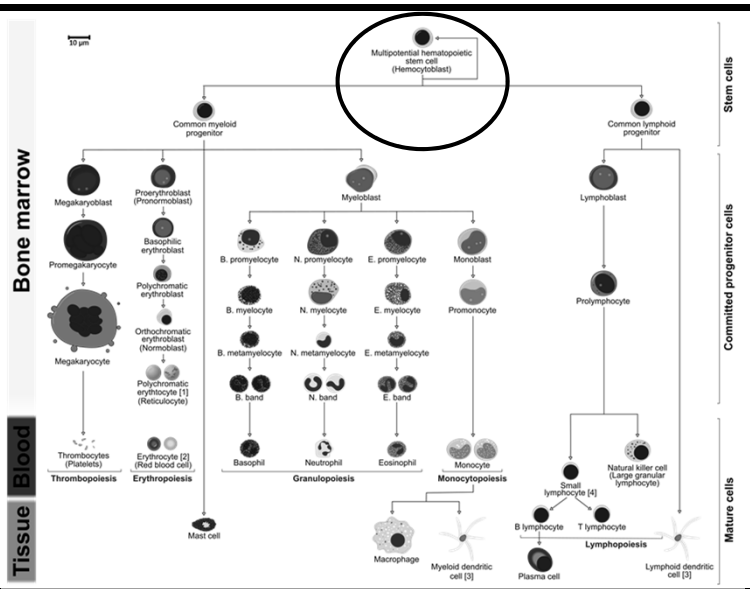
WHAT IS LEUKEMIA?

AMBIGUOUS LINEAGE ACUTE LEUKEMIA



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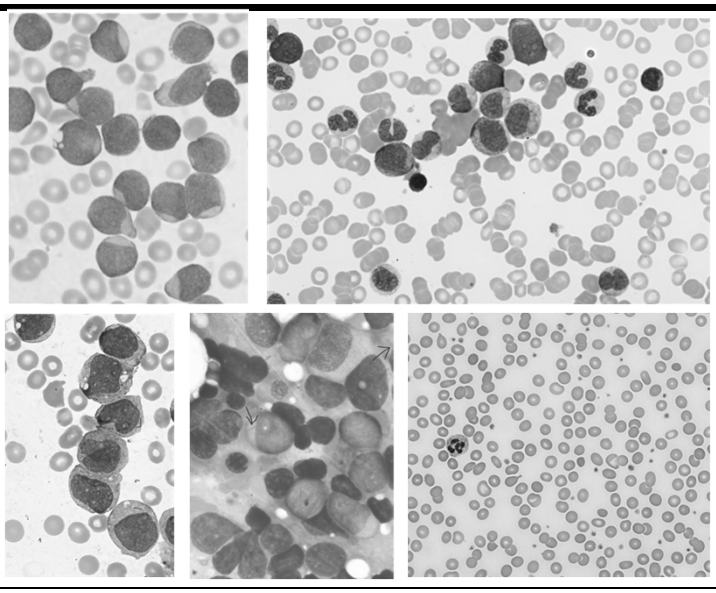
LEUKEMIA UNDER THE MICROSCOPE



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TESTING: BONE MARROW BIOPSIES

- Morphology
- Flow cytometry (immunophenotype)
- Cytogenetics
- Molecular genetics

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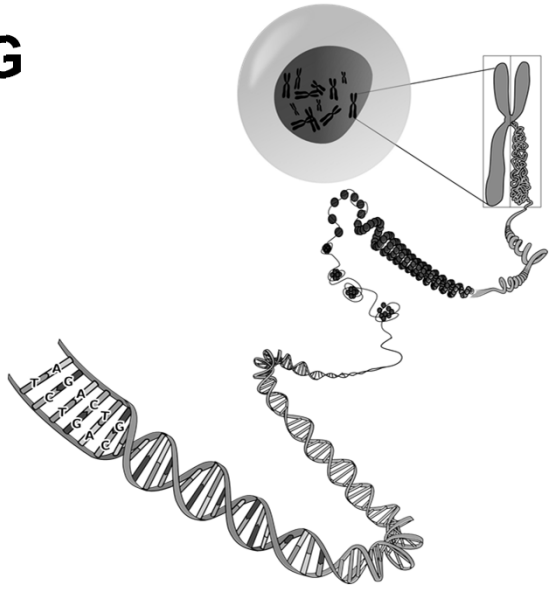
GENETIC TESTING

- Karyotyping
- Fluorescence in situ hybridization (FISH)
- Molecular genetics (next generation sequencing, NGS)



OTHER USEFUL TESTS/PROCEDURES

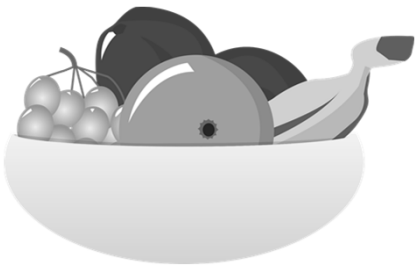
Testing	AML	ALL	CML
Lumbar puncture	If high suspicion	Multiple	No
PET or CT scans	Myeloid sarcoma	Presenting with LAD or masses	No
Tuneled line	Yes	Yes	No

LEUKEMIA

ACUTE VS. CHRONIC

In terms of:

- Prevelance
- Curability
- Acuity/Severity
- Treatment



EPIDEMIOLOGY

AML

- ~20,000 new cases yearly in US
  - > 11,000 deaths/year
- Median age: 68 years
- 5yr survival 30.5%

ALL

- ~ 6,600 new cases yearly in US
  - > 1,500 deaths/year
- Median age: 17 years
- 5 yr survival 70.8%

CML

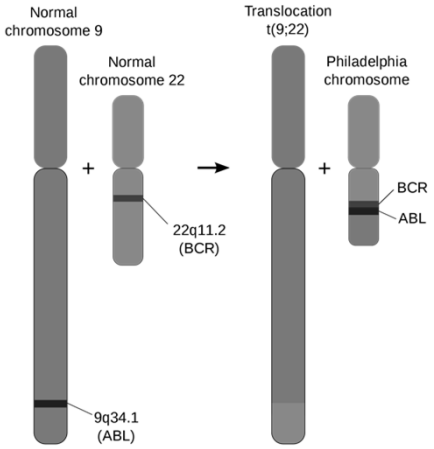
- ~8,800 new cases yearly in US
  - > 1,200 deaths/year
- Median age: 65 years
- 5yr survival 70.4%

SEER data. Cancer.gov

CHRONIC MYELOGENOUS LEUKEMIA

DIAGNOSING CML

- Clinical History
- Physical Exam
- Labs
- BCR-ABL
- BM Biopsy



SYMPTOMS

Up to 50% of patients asymptomatic
46-76% p/w splenomegaly
Fatigue, night sweats
Symptoms of anemia, bleeding d/t platelet dysfunction
<5% p/w hyperviscosity symptoms (usually WBC >250,000)

CBC AND PERIPHERAL SMEAR

Absolute leukocytosis (median 100,000)	Left shift
	Myelocytes outnumber mature metamyelocytes on PB smear
	Blasts usually <2%
	Absolute basophilia (100%)
	Absolute eosinophilia (90%)
	Platelet count usually normal or elevated
	Thrombocytopenia= alternative dx OR advanced stage CML

CML PHASES

Chronic	Accelerated	Blast
• most patients present in early phase	• more aggressive disease, less likely to respond as well to therapy • most commonly seen after treatment failure	• AML or ALL

CML RISK SCORES

Sokal

Hasford

European Treatment and Outcome Study (EUTOS)

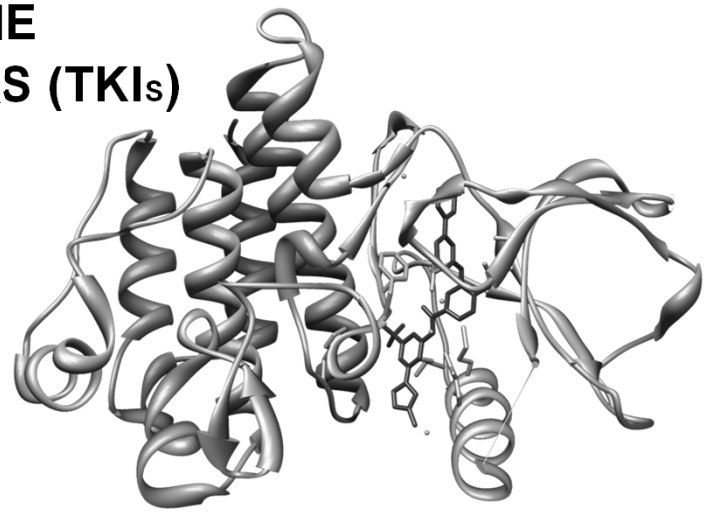
- Spleen size
- Cell counts
- +/- Age

→

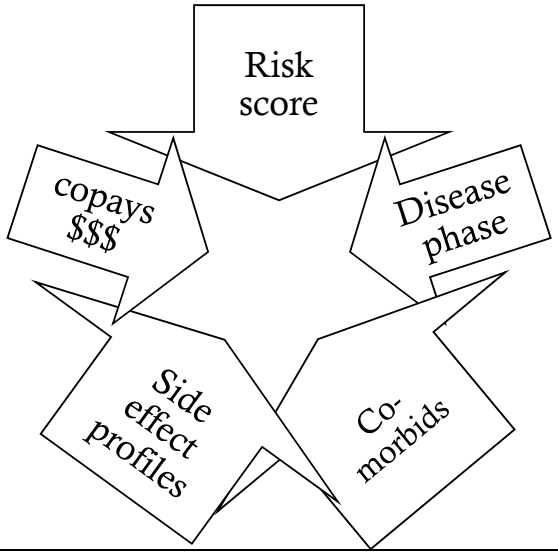
- Low
- intermediate
- high

BCR-ABL TYROSINE KINASE INHIBITORS (TKIs)

- **Imatinib (1998)**
- Dasatinib
- Nilotinib
- Bosutinib
- Ponatinib
- Asciminib



WHICH TKI TO CHOOSE?



MONITORING WHILE ON TKI THERAPY

CBCs --> complete hematologic response

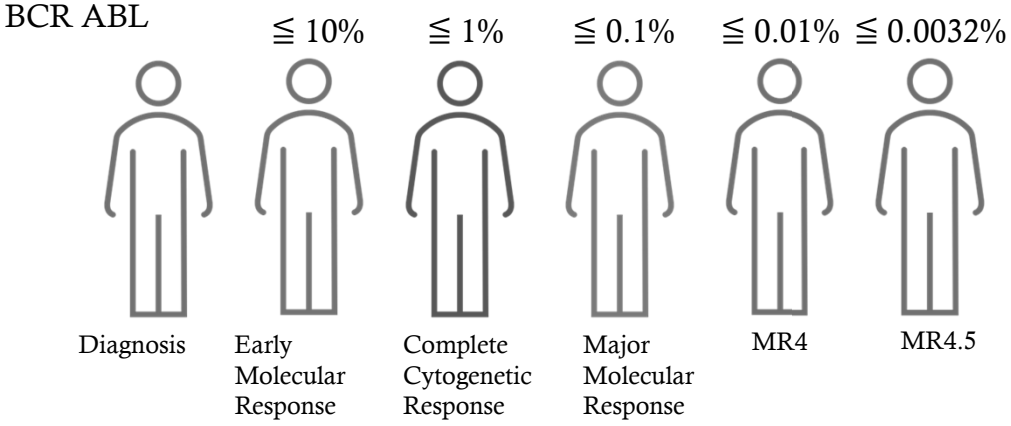
Quantitative PCR for BCR-ABL transcript q3 months

Exams/labs focused on side effect profiles

- Pleural effusions, pericardial effusions
- Pancreatitis
- CAD

"intolerable side effects"

MOLECULAR RESPONSE DEFINITIONS



INTOLERANCE TO TKI

Side effects	Can be numerous
	Often resolve with time
	Often managed with good supportive care
	Can require dose reductions or dose interruptions especially in the beginning
	Severity of some reactions can require permanent drug discontinuation

LOSS OF RESPONSE TO TKI

- Adherence
- Adherence
- Adherence
- Taking correctly (PPIs, food)
- Check TKI resistance panel
  - BCR-ABL kinase domain mutational analysis

TREATMENT FREE REMISSION

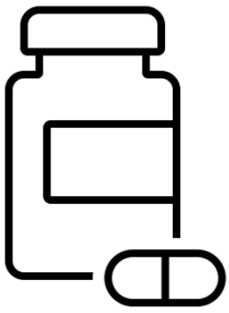
- Age >=18
- Prior to evidence of quantifiable BCR-ABL1 transcript
- Chronic phase CML
- No prior hx of Accelerated or Blast phase CML
- On TKI for >=3 years
- Stable molecular response
- MR4 (<=0.01%) for >= 2 years

MONITORING AFTER DISCONTINUATION

- Enhanced Monitoring off drug
  - First 6 months monthly
  - Second 6 months decrease to Q2 months
  - Forevermore Q3 months

Can continue to hold TKI as long as maintain MMR (<=0.1%)

SUCCESS?



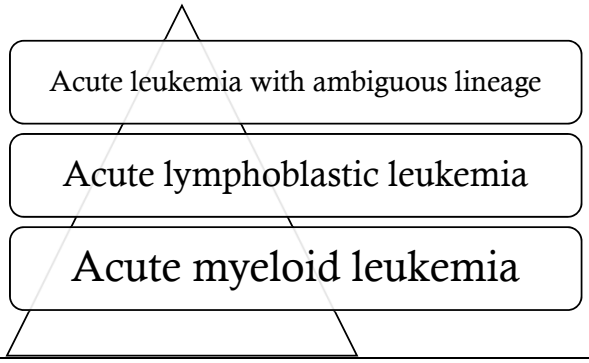
Majority of relapses will occur within 12 months of discontinuation

Roughly ½ patients will maintain a durable remission off of therapy

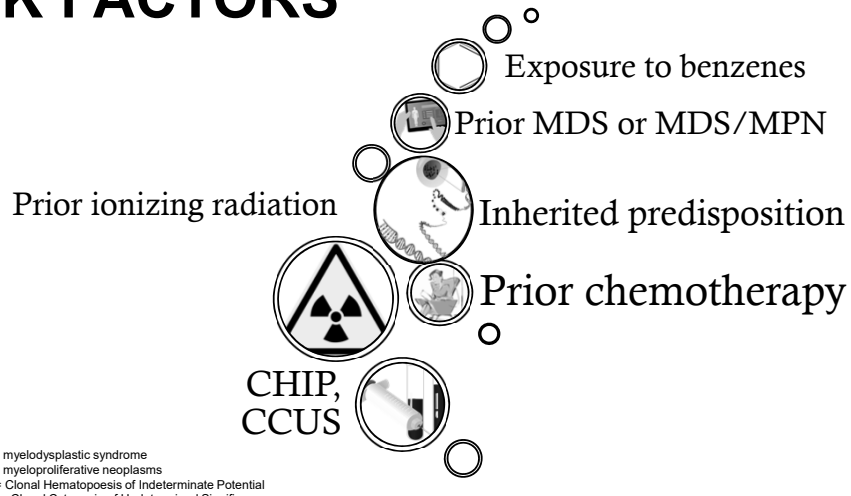
CML SUMMARY

- CBC and peripheral smear are very helpful in distinguishing
  - *Peripheral basophilia
  - PB looks like BM
- Diagnosis from PB t(9;22) and BM Biopsy establishes stage
- Multiple TKI treatment options- depends on disease factors/risk score, patient factors
- Can now consider discontinuing TKI with very close monitoring and follow up

ACUTE LEUKEMIAS



RISK FACTORS

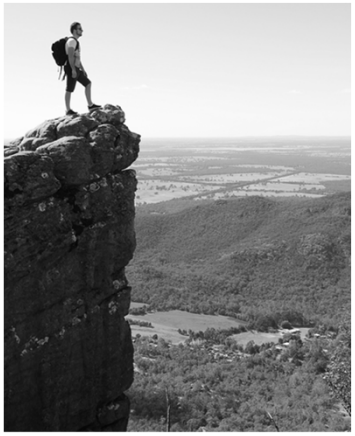


MDS = myelodysplastic syndrome
MPN = myeloproliferative neoplasms
CHIP = Clonal Hematopoesis of Indeterminate Potential
CCUS = Clonal Cytopenia of Undetermined Significance

DIAGNOSING ACUTE LEUKEMIA

- Peripheral smear to evaluate CBC differential and morphology
- Laboratory tests (LDH, uric acid, comprehensive metabolic panel, coags including fibrinogen), Immunophenotyping
- Bone marrow aspirate and biopsy
- +/- Lumbar Puncture and Testicular exam/US
- Genetic Testing

SYMPTOMS



Incredible range	Fatigue
	Fevers
	Infections
	DIC
	TLS
	hyperleukocytosis
	Bleeding/bruising
	Rash – petechiae, leukemia cutis
	gum hypertrophy
	myeloid sarcoma

CBC AND PERIPHERAL SMEAR

Profound cytopenias	Neutropenia
	Leukocytosis (predominantly blasts)
	possibly dysplastic neutrophils
	Anemia without schistocytes or other abnormal indices
	thrombocytopenia, no clumping

TREATMENT NOMENCLATURE

Induction

- Intensive chemotherapy for patients with active leukemia (hoping to "induce" remission)

Consolidation

- Treatment given to "consolidate" or deepen remission (hopefully into a cure)
  - *Chemo only*
  - *Allogeneic stem cell transplant*

Maintenance

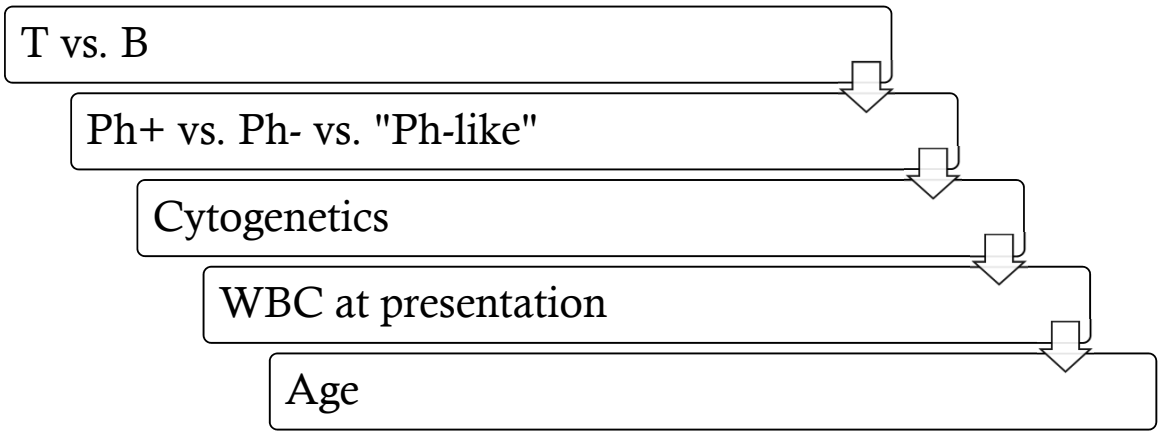
- Therapy given to prevent relapse once in remission

RESPONSE NOMENCLATURE

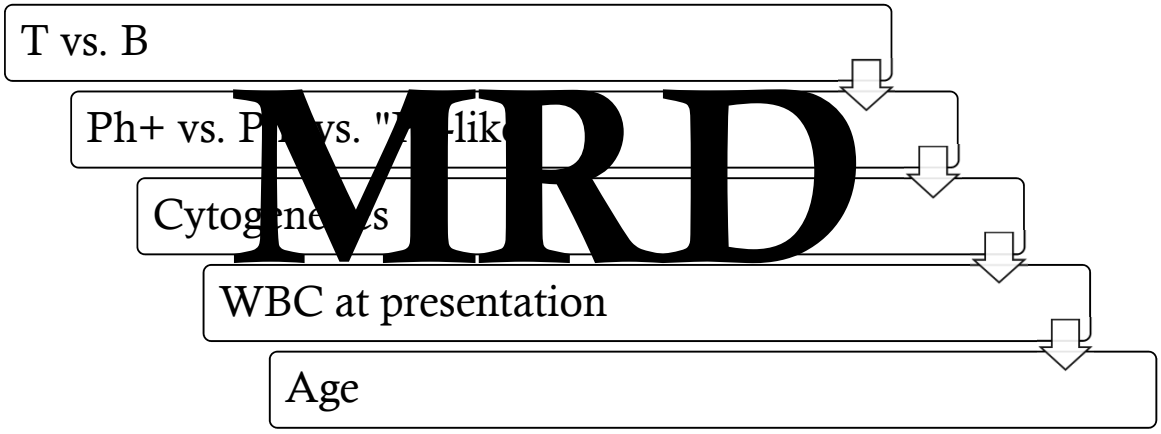
- Complete Response (CR)
- Complete Response with incomplete count recovery (CRi)
- Morphologic leukemia free state (MLFS)
- Remission ≠ Cure
- Minimal (Measurable) Residual Disease (MRD)

ACUTE LYMPHOBLASTIC LEUKEMIA

PROGNOSTICS

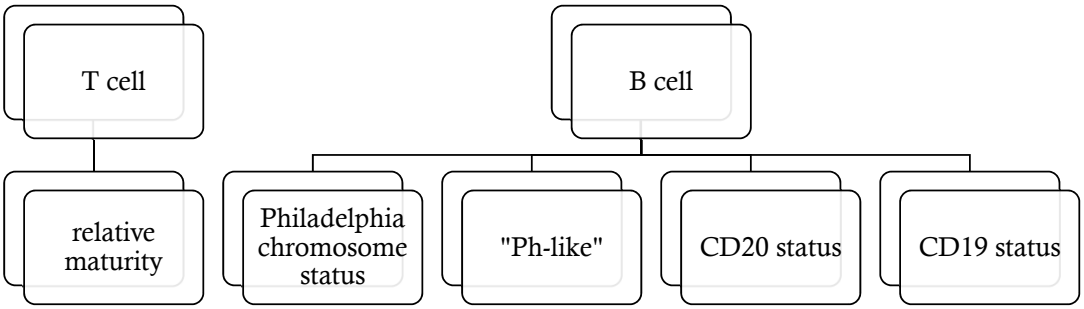


PROGNOSTICS



ALL THERAPEUTICS

Origin

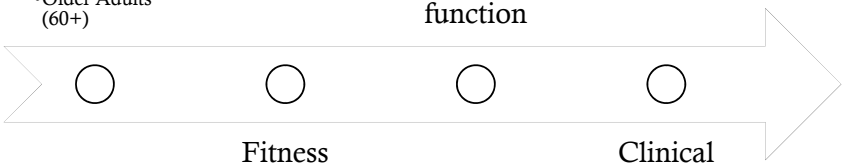


ALL THERAPEUTICS

Patient

Age

- AYA (15-39)
- Adult (40-60)
- Older Adults (60+)



Multi-agent chemotherapy regimens

TKIs

Antibody-drug Conjugates

Bi-specific Antibodies
CART

ACUTE MYELOID LEUKEMIA

PROGNOSTICS: EUROPEAN LEUKEMIANET 2022

Favorable

- Cure possible with chemo alone

Intermediate

- Broadest range of outcomes
- Allo SCT generally recommended

Adverse

- Uniformly poor outcomes
- Allo SCT if possible

PROGNOSTICS: EUROPEAN LEUKEMIANET 2022

Favorable

- Cure possible with chemo alone

Intermediate

- Broadest range of outcomes
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Adverse

- Uniformly poor outcomes
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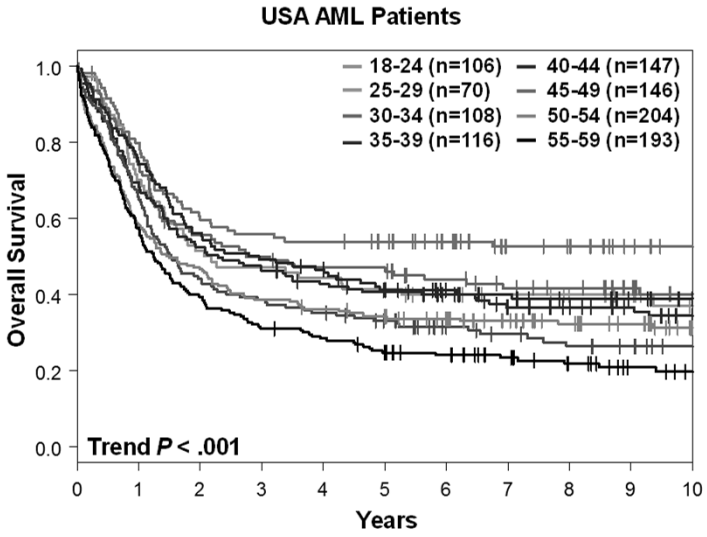
MRD

PROGNOSTICS

- **Age**
- Race
- Socioeconomics and other demographic data



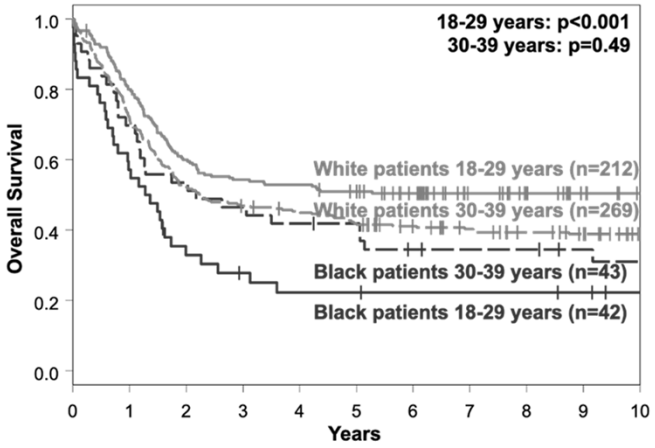
Data presented by Larkin et al at ASH 2021

PROGNOSTICS

- Age
- **Race**
- Socioeconomics and other demographic data

Overall survival

	18-29 years		30-39 years	
	Black patients	White patients	Black patients	White patients
OS Median (years)	1.3	10.2	2.2	2.2



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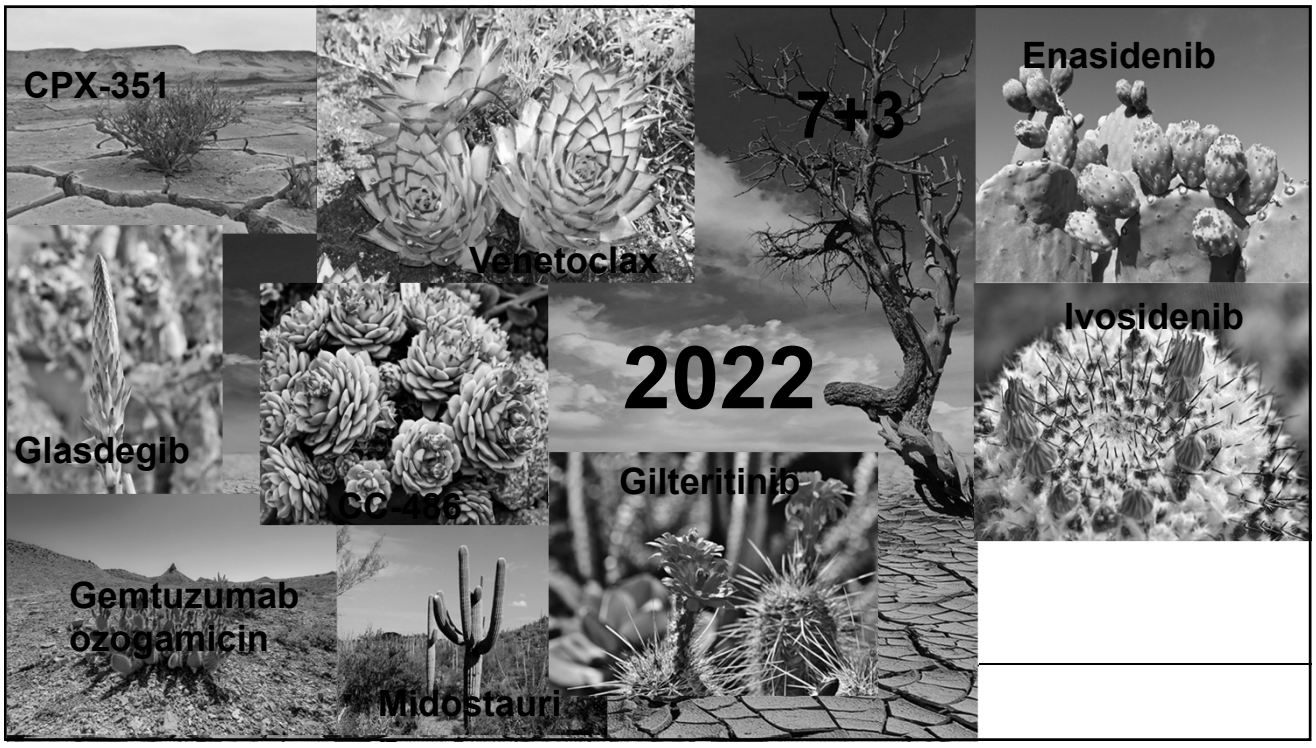
AML THERAPEUTICS



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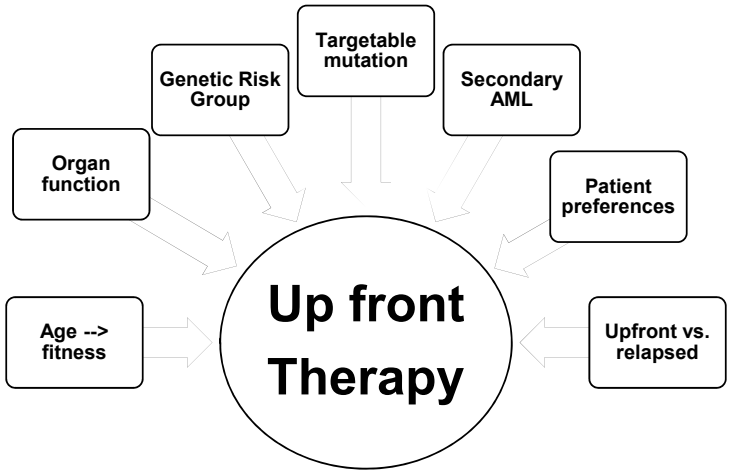

ADVERSE EFFECTS OF THERAPY

- Immediate and prolonged hospitalization*
- Direct toxicity from chemotherapy
- Infections due to immunosuppression
- Functional decline
- Transfusion needs
- Psychosocial stressors

AL SUMMARY

- Onset is typically rapid
- Key historical items can help raise your suspicion in some cases
- CBC and peripheral smear are very helpful in identifying this urgent/emergent disease
- Diagnosis requires multiple specialized tests
- Prognosis depend on multiple factors
- Treatment options are personalized

HIGH YIELD POINTS

How do you recognize leukemia?

- Patient presentations vary and sometimes require high degree of clinical suspicion
- CBC is very often enough obvious to direct further work-up

CML on TKIs

- Characteristic and non-characteristic side effects
- Adherence is key
- There is hope for treatment free remissions albeit in a minority of patients

Acute Leukemia is a rapidly changing field

- Diagnostics have become more complicated but improved
- Many more tolerable treatment options