LYMPHOMA

Cheryl Kovalski, DO, FACOI
ACOI BOARD REVIEW, 2018
no disclosures

- Solid neoplasm of the immune system characterized by uncontrolled proliferation of cells residing in the lymphoid tissues
- 2016 WHO revised classifications: 93 types

- HODGKIN DISEASE
- ALL OTHER LYMPHOMAS

NONHODGKIN LYMPHOMA (NHL): WHO CLASSIFICATION

- Low grade: Small lymphocytic and follicular small cleaved/follicular mixed. Affecting older people, presenting in advanced stage, indolent but incurable.
- Lymph nodes can wax and wane for years
- Survival of untreated disease-years

NHL: WHO CLASSIFICATION

- Aggressive (formerly known as Intermediate grade): follicular large cell, diffuse small cleaved/diffuse mixed/diffuse large cell.
- Firm, enlarging mass, +/- B symptoms
- Survival of untreated disease-months

NHL: WHO CLASSIFICATION
CLASSIFICATION

- High grade/Highly Aggressive: Immunoblastic, small non-cleaved, lymphoblastic, Burkitts. Wide age range, variable stage, 30-40% long-term remission with intensive treatment.
- Rapidly enlarging lymph node mass
- Survival of untreated disease-weeks

- Lymph node biopsy to evaluate architectural and cytologic features as well as adequate enough to do immunophenotyping.

- FINE NEEDLE ASPIRATE IS INADEQUATE!

NHL: DIAGNOSIS

- Laboratory: CBC, diff, CMP, LDH, SPEP, B2-microglobulin
- Radiography: CT chest/abdomen/pelvis
- PET
- Bone marrow biopsy
- LP with CSF analysis in pts with sinus, epidural, testis dz or those prone to have circulating tumor cells-Burkitts, lymphoblastic

ANN ARBOR STAGING SYSTEM

STAGING

I Involvement of 1 lymph node or 1 extralymphatic site (IE)

II Involvement of 2 or more lymph node regions or localized extralymphatic disease and involved lymph nodes on the same side of the diaphragm (IIE)

III Involvement of lymph node regions on both sides of the diaphragm, +/- localized extralymphatic disease (IIIE), spleen (IIIS), or both (IIIES)

IV Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues with or w/o LN involvement

A Asymptomatic

B Fever, night sweats and/or unexplained weight loss of 10% or more of body weight in past 6 months

Only used for Hodgkin lymphoma

Treatment

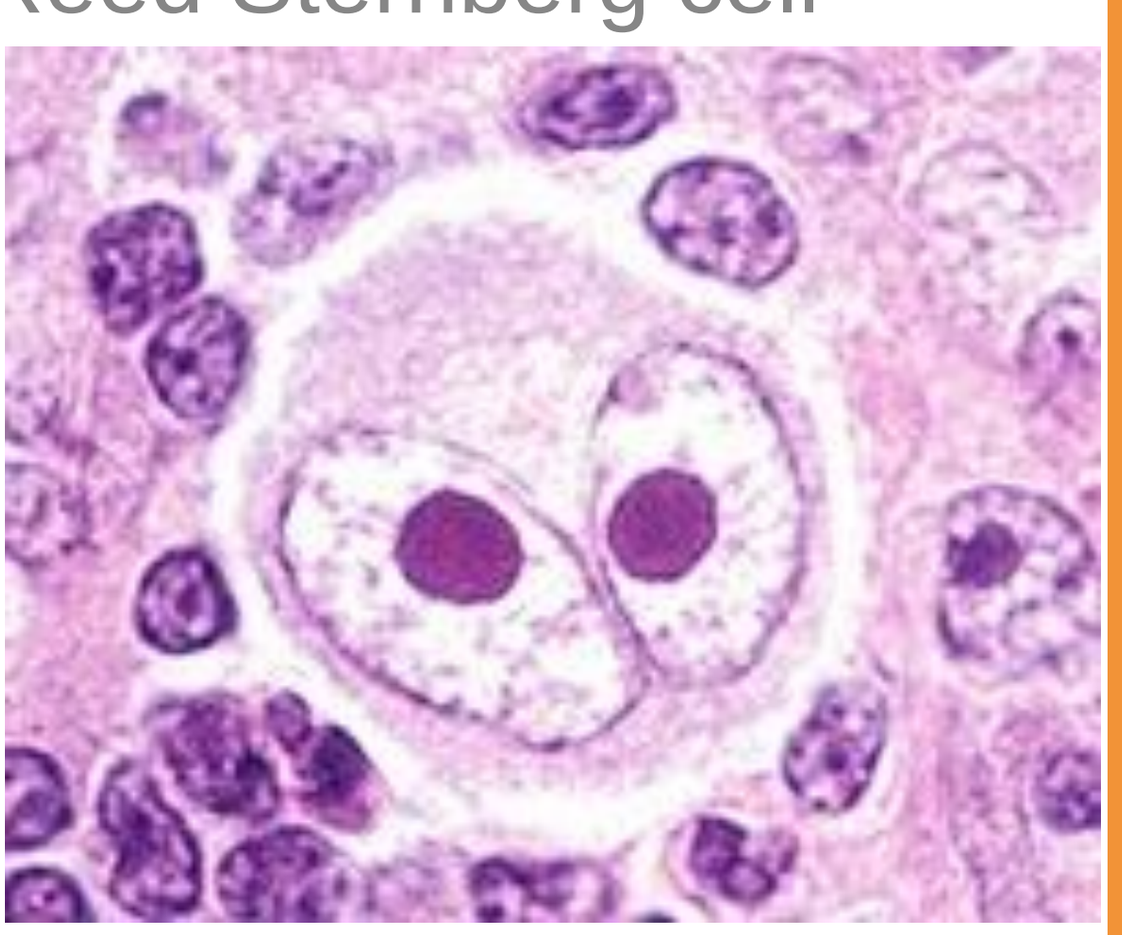
- Rituxan is added to treatment of B cell lymphoma that is CD 20 positive
- Low grade: Rituxan, bendamustine, CVP, CHOP
- Agressive grade: R-CHOP (cytoxan, adriamycin, oncovin, prednisone)
- Highly aggressive: Hyper CVAD, high dose methotrexate

HODGKIN DISEASE

- 1% of all malignancies in US
- First malignancy to demonstrate curative potential of combination chemotherapy
- Most common in young adults; bimodal peak in 3rd and 7th decades
- Association with Epstein-Barr virus
- Arises from B lymphocytes

- Differentiated from other lymphomas by the presence of large binucleate or multinucleate cell, Reed Sternberg cell

(Giant “owl eyes”)



HODGKIN DISEASE

- Nodes are painless and rubbery, most commonly found in neck and mediastinum
- Most common etiology of mediastinal mass in young person
- Unusual symptoms of pruritus, alcohol-induced pain in involved lymph node sites, sweats, fevers; intermittent “Pel-Ebstein” fever rare

HD: HISTOPATHOLOGIC SUBTYPES

- Lymphocyte Predominant
- Nodular Sclerosis
- Mixed Cellularity
- Lymphocyte Depleted

- Nodular lymphocyte predominant

HD: POOR PROGNOSTIC FACTORS

- Advanced Stage
- Large mediastinal mass (ratio>0.33)
- Systemic symptoms
- Extra nodal disease
- Advanced age
- Male sex

HD: TREATMENT

- Favorable Stage I and IIA: 2-4 cycles chemotherapy and involved field RT
- Limited HD with risk factors: Full chemotherapy & involved field RT
- Advanced HD: Full chemotherapy and RT only for pts with bulky mediastinal disease
- Bone marrow transplant usually considered after first relapse
- ABVD is standard regimen (adriamycin, bleomycin, vinblastine, dacarbazine)

HD: LATE EFFECTS OF TREATMENT

- Mantle RT: hypothyroid, heart disease
  lung & breast cancer
- Para-aortic or splenic: gastric cancer
- MOPP chemotherapy: acute leukemia
  sterility

HODGKINS SURVIVAL

- STAGE
- IA-IIA 80-90 %
- IB-IIB 80-85 %
- IIIA 75-80 %
- IIIB 60%
- IVA-B 60%

LEUKEMIA

no disclosures

ABNORMALITIES OF CELLULAR PROLIFERATION IN AL

	Normal	Leukemic
Stem Cells	Normal	Abnormal
Maturation	Synchronous with proliferation; terminates division	Asynchronous Does not terminate division
Feedback	Controls production	Absent or ineffective
Steady State	Yes	No
Release	Orderly	Random
End Product	Mature cells-cannot resume division	Immature cells-can resume division

LEUKEMIA CLASSIFICATION

ACUTE : LYMPHOCYTIC NONLYMPHOCYTIC

CHRONIC : LYMPHOCYTIC MYELOGENOUS

ACUTE LEUKEMIA

A DIVERSE GROUP OF NEOPLASMS ARISING FROM TRANSFORMATION OF UNCOMMITTED OR PARTIALLY COMMITTED HEMATOPOIETIC STEM CELLS

ACUTE LEUKEMIA PATHOGENESIS

- Leukemic cell abnormalities: cytogenetic abnormality leading to clonal proliferation of leukemic cell; maturation arrest of leukemic cells

- Leukemic cells inhibit normal cell lines from proliferating leading to : anemia, bleeding, infection; electrolyte imbalance; leukostasis

- Invasive & infiltrative effects

ACUTE LEUKEMIA: PRESENTATION

- Symptoms of only a few weeks duration
- Symptoms reflect bone marrow failure +/- involvement of extramedullary sites
- Fever, documented infections in up to half
- Symptomatic anemia
- May have bleeding, but hemorrhage rare
- Bone pain, fatigue

ACUTE LYMPHOCYTIC LEUKEMIA

- Mainly occurs in children- peak ages: 2-8, >60
- Worse prognosis with: increasing age
- Philadelphia chromosome
- WBC >30K
- Sex: equal
- Rare in blacks

ALL-PREDISPOSING FACTORS

- Irradiation early in life
- Ataxia telangiectasia
- Mongolism
- Leukemia in family
- Identical twin

ALL FAB CLASSIFICATION

FAB Class	Cell Size	Nucleus	Cytoplasm
L1	Small hoogeneous	Round, occasional cleft or fold; homogeneous, finely dispersed chromatin; nucleoli small or not visible	Usually scanty slight to moderate basophilia
L2	Large heterogeneous	Fine to coarse chromatin; clefts 1 or more nucleoli	Abundant, variable basophilia
L3	Large homogeneous	Oval to round, dense finely stippled chromatin; 1 or more prominent nucleoli	Moderately abundant, intensely basophilic , prominent vacuoles

ACUTE LYMPHOCYTIC LEUKEMIA: PRESENTATION

- Half have hepatomegaly, splenomegaly &/or lymphadenopathy
- Mediastinal masses primarily in T cell lineage ALL
- <10% with CNS involvement
- Other sites of extramedullary involvement: testis, retina, skin, any organ infiltrated

ALL: ADDITIONAL CLINICAL FEATURES

- C ALL: most common in children; lymphadenopathy common; gum, skin, mediastinal infiltration uncommon; muramidase staining-low or normal

- T cell ALL: most common in 2nd & 3rd decades; blasts more common in blood; frequent extra medullary disease-CNS, mediastinum

- B cell ALL: no distinct findings; responds poorly to conventional therapy

- Ph-positive ALL: shorter remissions than C ALL

ALL: GOOD PROGNOSTIC FEATURES

- Age less than 35 (best 3-9)
- WBC < 30,000
- Blasts < 80%
- Early complete remission after start of chemotherapy
- Absence of translocations
- Presence of hyperdiploid state
- CALLA+ phenotype
- Female

DIAGNOSIS

- Lymphoblasts seen on blood smear and bone marrow

  May be difficult to distinguish from myeloblasts

  Flow cytometry helpful in differentiating ALL from AML

- Evaluate CSF for CNS involvement

ALL: TREATMENT

- Daunorubicin, Vincristine and Corticosteroids are key drugs in induction
- Maintenance therapy at least 2 years
- CNS Prophylaxis
- Imatinib in Ph+ with chemotherapy
- Radiation in bulky mediastinal disease
- SCT if poor prognostic features or progressive disease

ACUTE NONLYMPHOCYTIC LEUKEMIA

- Group of marrow based malignancies, clinically similar, BUT DISTINCT morphologically, immunophenotypically, and cytogenetically
- Must distinguish from ALL
- More common in adults

AML FAB CLASSIFICATION

FAB Class	Predominant cell type
M1: undifferentiated myelocytic	Myeloblasts
M2: myelocytic	Myeloblasts, promyelocytes, myelocytes, blasts
M3: promyelocytic	Promyelocytes, blasts
M4: myelomonocytic	Promyelocytes, myelocytes, proonocytes, monocytes, blasts
M5: monocytic	Monoblasts, myeloblasts
M6: erythroleukemia	Erythroblasts, myeloblasts
M7: megakaryocytic leukemia	Abnormal appearing megakaryocytes myeloblasts

ANLL RISK FACTORS

- Exposure to ionizing radiation
- Exposure to chemicals: benzene, chloramphenicol, phenylbutazone
- Exposure to drugs: alkylating agents and topoisomerase II inhibitors
- Genetic factors: Mongolism, Bloom’s syndrome, Fanconi’s anemia
- MDS, Myelofibrosis, Polycythemia, CGL

ANLL PROGNOSTIC FACTORS

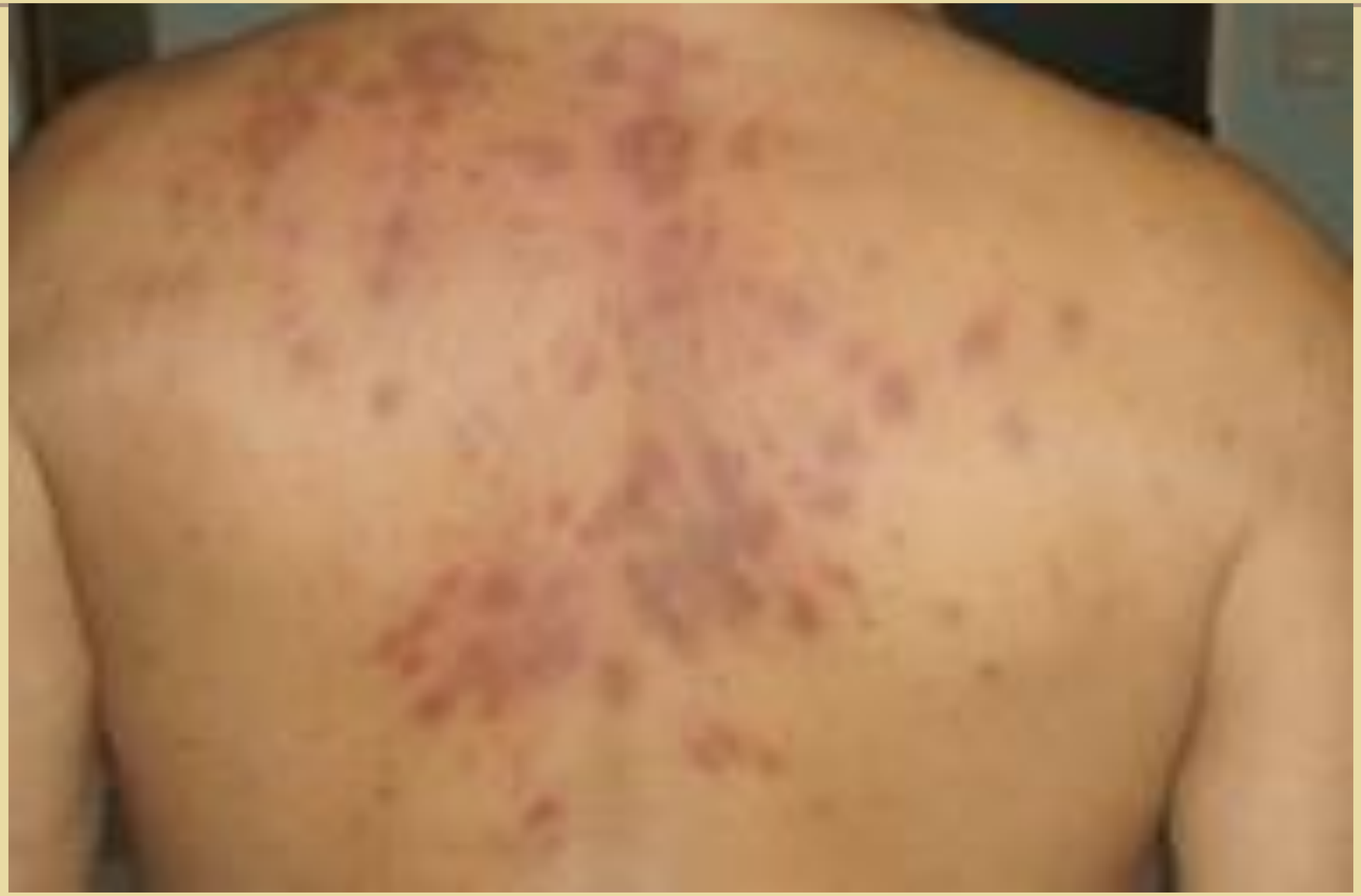
Worse if

- Age>60
- Poor performance status
- AML secondary to prior chemotherapy or bone marrow dysfunction
- WBC > 20K

CLINICAL FEATURES

- S & S secondary to anemia, thrombocytopenia, leukopenia or leukocytosis
- Hyperleukocytosis (>100K blasts): most common in hyper granular APL causing obstruction, vascular injury and hypoxia (due to pulmonary congestion) & ischemia increasing risk of stroke
- Coagulation abnormalities: abnormal platelet function; consumption (DIC)-M3>M4 or M5
- Typhilitis-mimics appendicitis
- Metabolic abnormalities: tumor lysis syndrome; renal tubular dysfunction
- Extramedullary : granulocytic sarcoma-M5, soft tissue involvement-skin, gingiva, lungs, lymph nodes(splenomegaly uncommon), CNS: headache, mental status change, nerve palsy

GRANULOCYTIC SARCOMA



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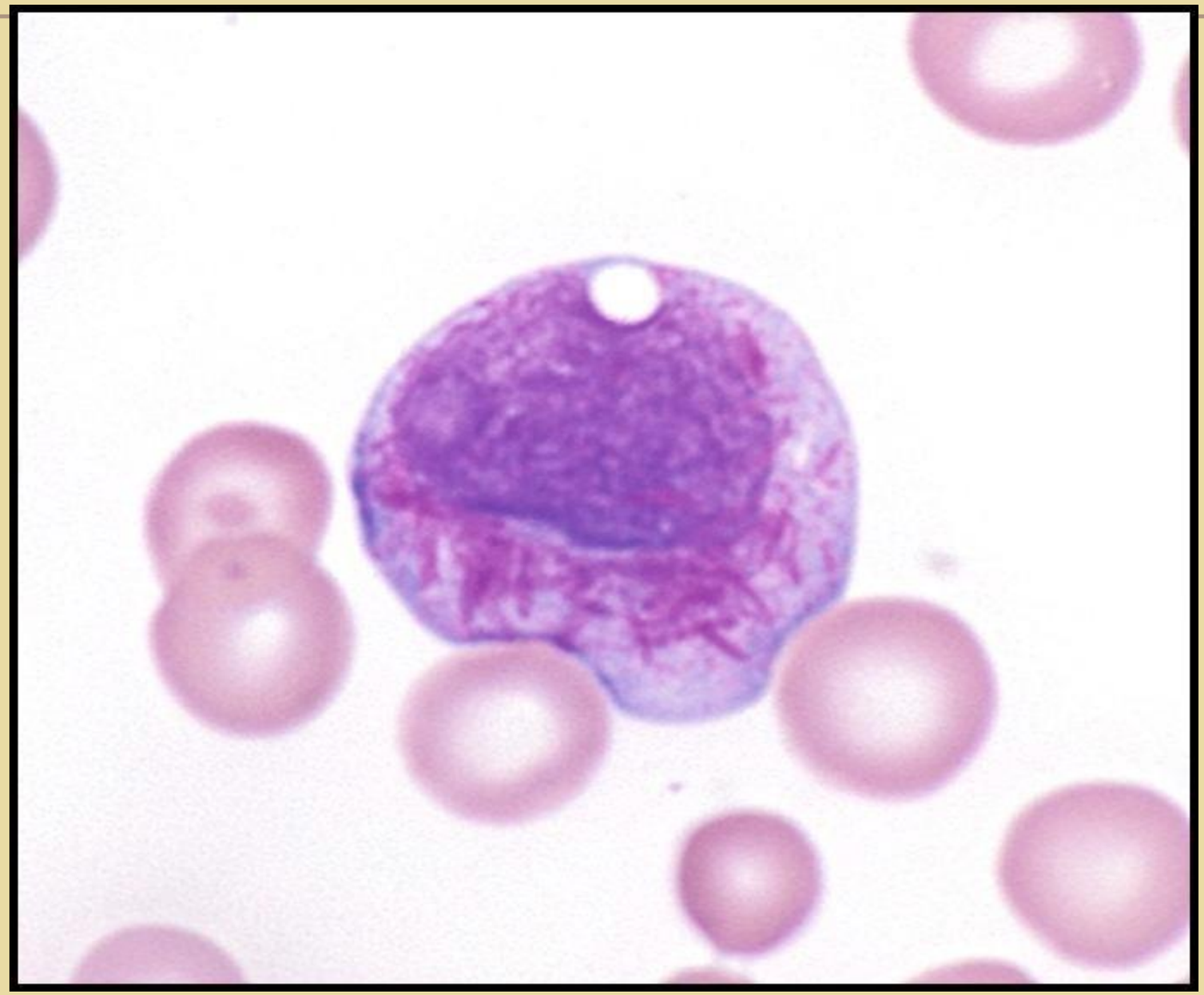
ANLL: LABORATORY FEATURES

- Anemia universally present; reticulocyte count low
- Thrombocytopenia nearly always present (decreased production & survival)
- Leukopenia in 20% with absolute neutropenia
- Leukocytosis >50%; myeloblasts almost always present in blood
- Auer rods <10%

AUER RODS



ANLL: BONE MARROW FINDINGS

- Blasts
- Decrease in normal blood cell progenitors
- Cytogenetics performed to identify any genetic abnormality diagnostic of a particular FAB class
- Immunophenotyping

ANLL: IMMUNOPHENOTYPE

- May help establish diagnosis, more precise than morphology alone
- Distinguishes ALL from ANLL, identifies subtypes, recognizes biphenotypic
- Characteristic ANNL: CD 13 & 33+
- Often CD 11& 14+
- CD34 unfavorable
- Lymphoid markers may be expressed

ANLL: TREATMENT

- Address concurrent medical problems

- Supportive care:

-Blood product transfusion

-Broad spectrum antibiotics for fever and neutropenia

-Antifungal & antiviral therapy

-Nutrition

ANLL: THERAPY

- Remission induction: 7+3 regimen: ARA-C + daunorubicin= 60-80% CR

- Postremission therapy:

  -Consolidation with Ara-C

  -Allogeneic SCT

- APL: ATRA + chemotherapy

CHRONIC LEUKEMIA

no disclosures

CHRONIC LYMPHOCYTIC

Most common leukemia in Western world

Median age at diagnosis: 65

Median survival: 9 years

Advanced disease has increased morbidity and mortality from infection: T cell dysfunction, lack of ability to make Ig, results of treatment

CLL: DIAGNOSIS

- Lymphocytosis (ALC> 5000) small, mature lymphocytes
- Bone marrow involvement >30% lymphs
- < 55% atypical/immature lymphoid cells in peripheral blood
- Clonal expansion of abnormal B lymphs
  -B-cell surface ags (CD 5, 19, 20, 23)

CLL: CLINICAL COURSE

- Incidental finding of lymphocytosis
- Asymptomatic at time of diagnosis and for a prolonged period of time

CLL CLINICAL COURSE

- Progressive bone marrow impairment
- Progressive neutropenia and hypogammaglobulinemia increasing risk of infection
- Autoimmune phenomena
- Richter's transformation

CLL: AUTOIMMUNE COMPLICATIONS

- Coombs' + hemolytic anemia in 15%
- ITP
- Pure red cell aplasia
- Granulocytopenia

CLL: RAI STAGING

Stage	Risk	Features	Surv yr
0	Low	Lymphocytosis	> 12
I	Intermediate	Adenopathy	8
II	Intermediate	Splenomegaly +/- Hepatomegaly	6
III	High	Anemia	1.6
IV	High	Thrombocytopenia	1.6

CLL: POOR PROGNOSIS

- Advanced stage at diagnosis
- Short lymphocyte doubling time (6 mos)
- Diffuse pattern of marrow infiltration
- Advanced age/male
- 17p or 11q deletion
- High serum levels of B2 microglobulin and CD23
- CLL-PLL
- Richter's syndrome

CLL TREATMENT

- Incurable
- Observation is appropriate for early stage or asymptomatic CLL
- No proven advantage to early chemotherapy if asymptomatic

CLL: INDICATIONS FOR TREATMENT

- B Symptoms secondary to CLL: weight loss >10%, night sweats, fever
- Progressive marrow failure
- Massive splenomegaly
- Massive lymphadenopathy

CLL: INDICATIONS FOR TREATMENT

- Progressive lymphocytosis, >50% increase over 2 mos or lymphocyte doubling time <6 mos
- Richter's syndrome-transformation from low to high grade lymphocytic malignancy
- Hemolytic anemia
- ITP

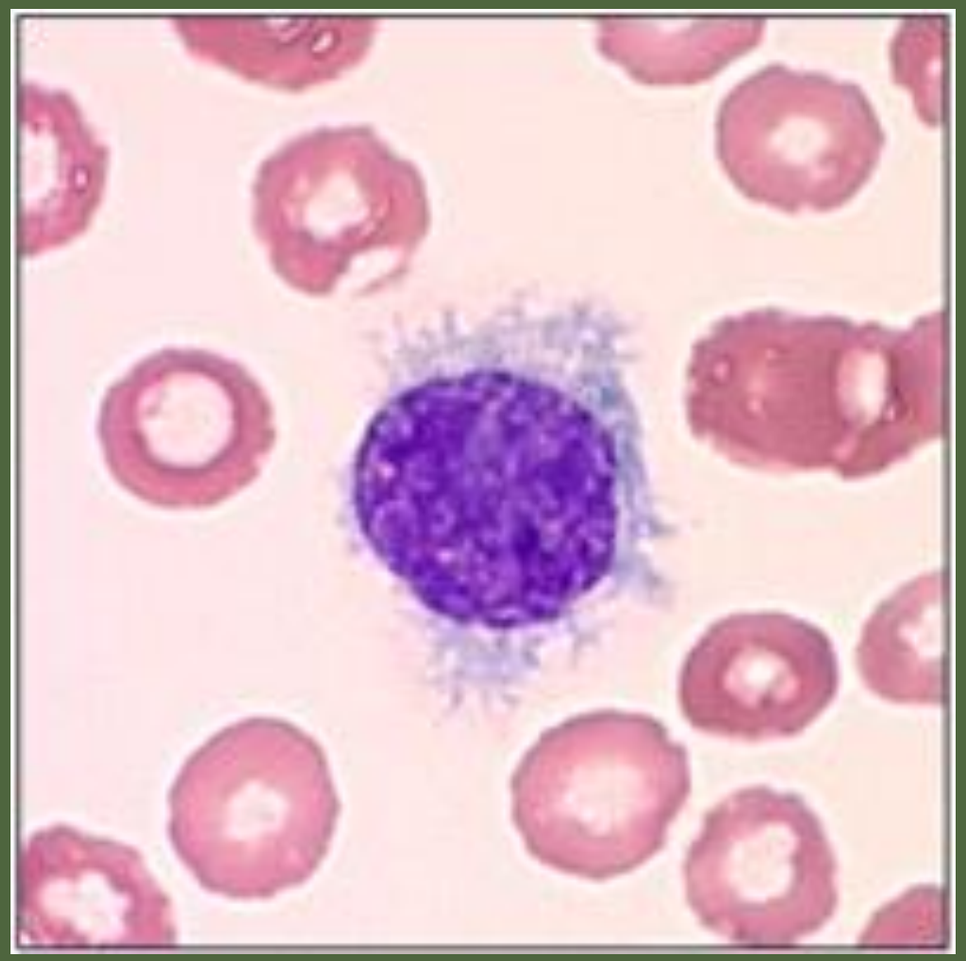
CLL: TREATMENT

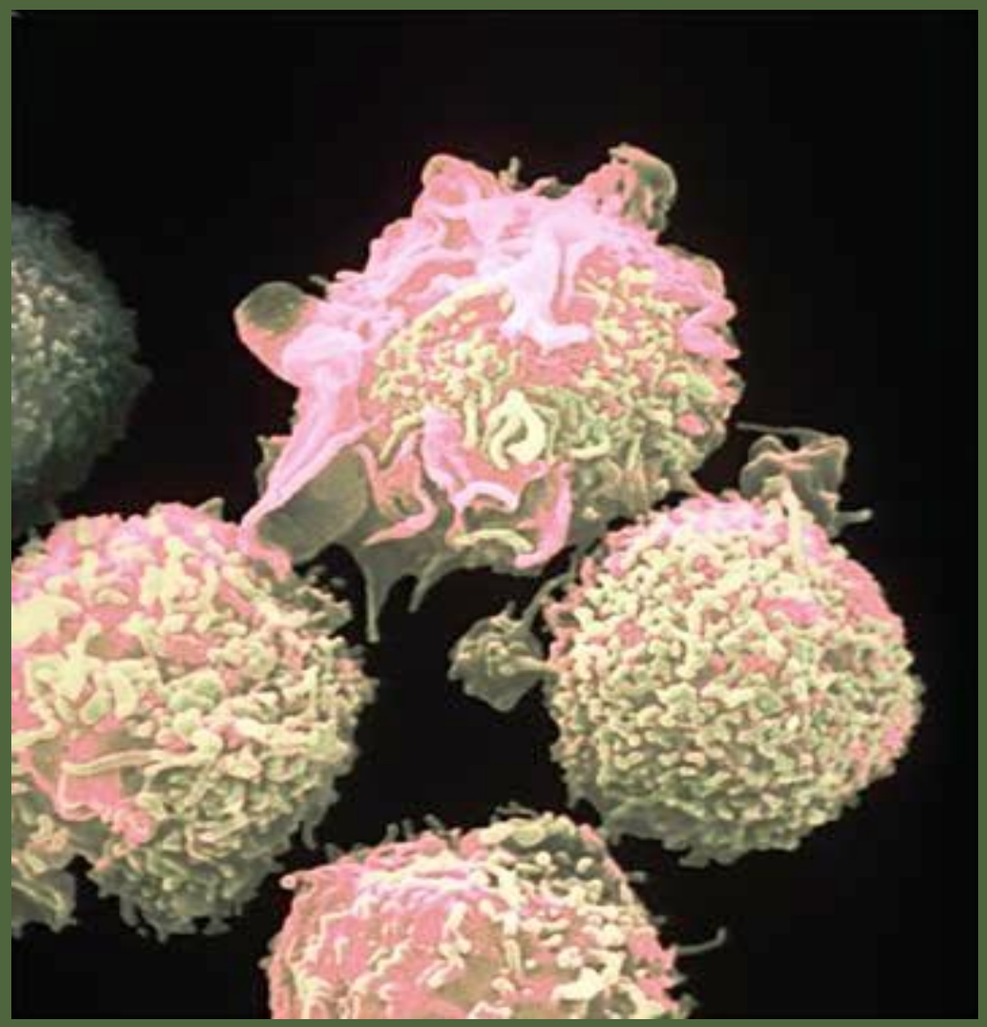
- Alkylating agents: bendamustine, chlorambucil
- cyclophosphamide
- Corticosteroids
- Purine analogs: fludarabine
- cladribine, pentostatin
- Monoclonal abs: Rituximab, Alemtuzumab
-

HAIRY CELL LEUKEMIA

- Rare B-cell leukemia
- Median age of onset: 55
- Strong male predominance
- Presents with pancytopenia and massive splenomegaly
- Characteristic "dry tap" bone marrow due to hypercellularity

HAIRY CELL LEUKEMIA





HAIRY CELL LEUKEMIA

- TRAP +
- Treatment with 2-CDA (cladribine) or Pentostatin induces complete remission in most

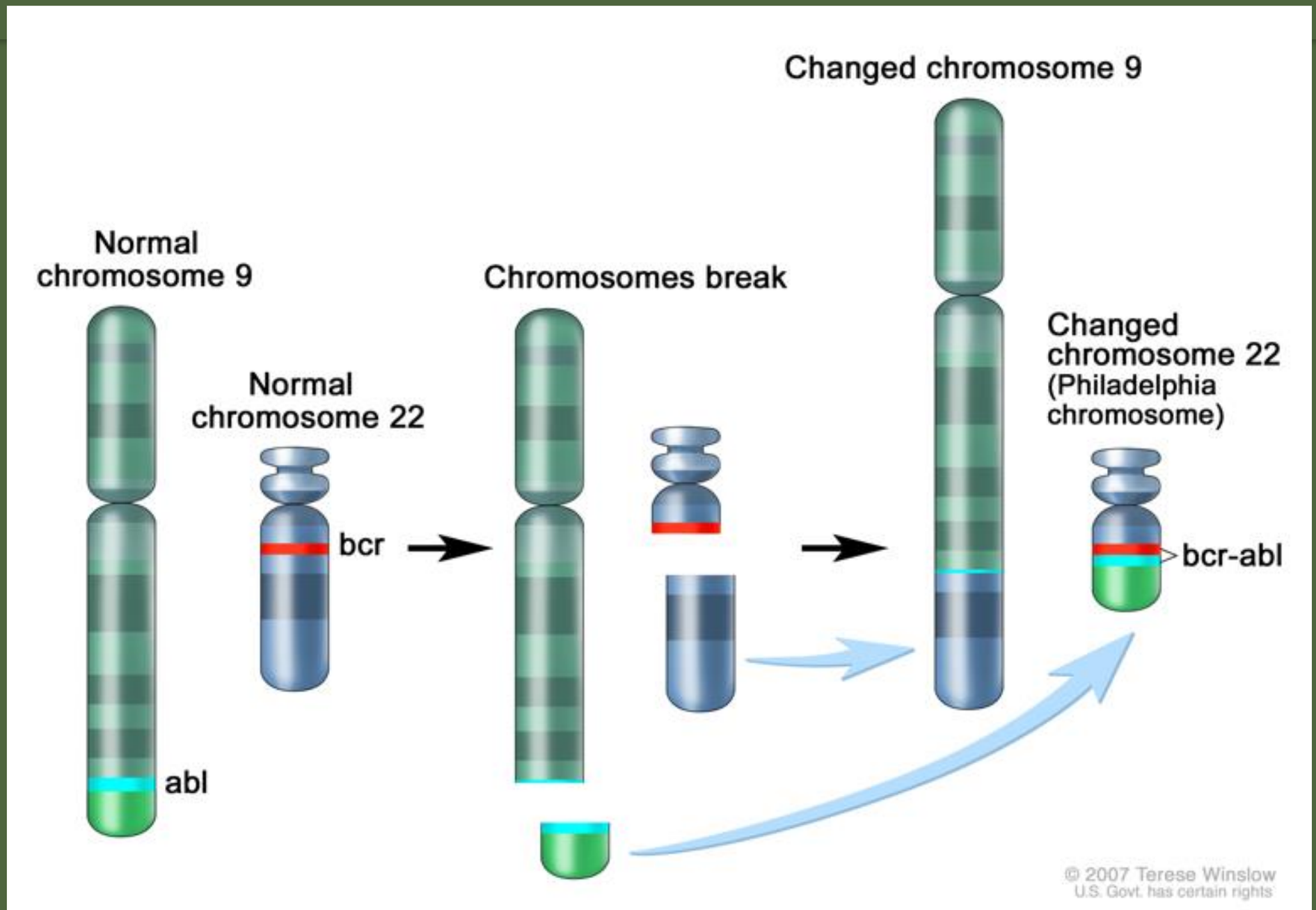
CHRONIC MYELOGENOUS LEUKEMIA

- Clonal myeloproliferative disorder of pluripotent stem cells affecting all cell lines
- Cytogenetic hallmark: Philadelphia chromosome (9;22)
- Molecular hallmark: BCR/ABL
- 7-15% adult leukemias
- Median age: 45-55; 20-30% >60

CML: PRESENTATION

- 85% in chronic phase at diagnosis
- 5% Ph negative
- Symptoms:
- -Most asymptomatic, only leukocytosis
- -LUQ discomfort and early satiety secondary to splenomegaly
- -Unusual infections

PHILADELPHIA CHROMOSONE



PHILADELPHIA CHROMOSONE

Translocation 9;22 = BCR-ABL rearrangement

Leukemia phenotype	Incidence
CML	95%
ALL	25-30% adult
	5% children
AML	1-2%

CML Phases

	Chronic	Accelerated	Blastic
Past	3-5 years	12-18 months	3-9 months
Present	25+ years	4-5 years	6-12 months
	Asympto-matic	Blasts >/= 15% Bl+Pros >29% Basophils>19%	Blasts >29%
		Platelets <100K Clonal evolution	extrmedullary disease with localized immature blasts

CML WORK-UP

Physical exam: performance status, splenomegaly

CBC, diff, chem pro

Bone Marrow

Cytogenetics

CML: CURRENT TREATMENT RECOMMENDATIONS

Frontline:

Imatinib, Nilotinib, Dasatinib

Imatinib failure: nilotinib, dasatinib, bosutinib

Allogeneic SCT