

## HEMATOLOGIC NEOPLASIA LECTURE I

**LN** = lymph node      **CD** = cluster designation of leukocyte antigen

### **I. What is the clinical problem ?**

Neoplasms of the hematologic system comprise ~8 % of malignancies, and account for ~9 % of all cancer deaths in Maryland. In children and young adults they are the most common cause of death from neoplasia. As a general rule; however, the overall incidence hematologic malignancies increases with age. The prognosis for patients with these diseases is variable and depends upon the specific diagnosis. Some of hematologic neoplasms can be cured, others progress very slowly and can be treated for 10-15 years before the patient succumbs. In other cases the disease resists treatment and is rapidly fatal.

**For the patient and physician, the key to predicting tumor behavior and planning therapy is an accurate classification.**

### **II. What is the pathogenesis of these neoplasms?**

Excessive exposures to gamma radiation or toxic chemicals clearly can be associated with an increased risk of malignancies with myelocytic phenotypes. Abnormal function of growth factor receptors is also implicated. The incidence of malignancies with lymphocytic phenotypes has been rising. Factors implicated include: (1) population ageing, (2) increased use of immunosuppressive therapies, and (3) HIV infection with immunosuppression. Infections by viruses of the herpesvirus family (EBV, KSHV) have been associated with lymphocytic malignancies.

Many genetic changes occur during the process of hematologic neoplasia; however, the specific factors which drive the genetic changes and cause emergence of neoplastic phenotypes are not fully understood. Certain chromosomal translocations can be a cause of growth promotion or the extended survival of neoplastic cells.

### **III. What types of cells are involved?**

Most of the hematologic neoplasms represent clonal expansions of either an abnormal pluripotent stem cell (CD34 cells) or a multipotent precursor from one of the major hematologic lineages. Immunophenotyping or molecular analyses

often reveal abnormal admixtures of surface CD antigens or other markers which would not be expected at the same time or in the same cell type under normal conditions of lineage maturation. This is "lineage infidelity". As a neoplasm progresses, the expressed phenotype may prove unstable and change. Therefore **neoplastic hematopoietic cells can never be exactly matched to normal hematopoietic counterparts.**

#### **IV. How is a diagnosis of hematologic neoplasia determined ?**

In practice, diagnostic classification depends upon the clinical picture as well as the cell and tissue findings. Clinical criteria include the patient's age, tumor anatomic location or distribution and the pattern of cellular growth and spread. Detection of surface CD antigens by flow cytometry is an important auxiliary to microscopic study of cell size, nuclear features, cytoplasmic granules or inclusions, and cytochemistry. Chromosomal translocations or duplications are determined by karyotyping or FISH). Molecular diagnostics may include PCR or Southern blots. **Most recently microarray techniques for examining patterns of tumor gene expression have proven to be powerful tools for separating categories of lymphocytic malignancies.** As the technologies improve accuracy of classification, medical researchers will be able to gain a better understanding of pathogenesis and customize therapies.

#### **V. Why does the diagnosis often require special expertise.**

Classifications, and terminologies for neoplasms of myelocytic phenotype have been stable for many years and pose little problem for clinicians or medical students. Due to rapidly advancing knowledge, classifications of the neoplasms with lymphocytic phenotypes have been in a state of flux. Despite frequent changes in nomenclature, clinical experience has taught that the most common forms of lymphocytic malignancies have typical physical presentations and tend to affect particular age groups. These points will be emphasized in lecture.

#### **VI. What are the major clinical-pathologic entities I should know about ?**

##### **myelocytic lineage and phenotypes**

##### **A. Myelodysplastic syndrome (MDS)**

a benign atypia of erythrocytes, granulocytes or platelets

***patients have a high risk of developing myelocytic leukemia***

##### **B. Myeloproliferative disease**

benign neoplastic proliferation of abnormal stem cells - usually express as erythroid or megakaryocytic phenotypes

***patients have a high risk of developing myelocytic leukemia***

**C. Myelocytic leukemias**

malignant clonal proliferation of a stem cell which gives rise to circulating cells of myeloid phenotype.

**lymphocytic lineage and phenotypes**

**D. Lymphocytic leukemias**

malignant clonal proliferation of a stem cell which gives rise to circulating cells of lymphocytic phenotype

**E. Lymphocytic solid tumors**

malignant clonal proliferations of cells which arise in lymph follicles or lymph nodes and show a lymphocytic phenotype

<u>Non-Hodgkin lymphomas</u>	predominantly B cell phenotypes
B cells of Reed-Sternberg type	<u>Hodgkin's disease</u> - usually
<u>Plasma cell neoplasms</u>	Ig secreting B cells

**dendritic cell lineage and phenotype**

F. Langerhans cell histiocytosis (histiocytosis X)

**HEMATOLOGIC NEOPLASIA - MYELOID LINEAGE**

**LAP** = leukocyte alkaline phosphatase found in granules of mature neutrophils    **TdT** = terminal transferase involved in DNA elongation

**I. CONDITIONS WITH A HIGH RISK OF DEVELOPING LEULKEMIA**

**A. APLASTIC ANEMIA OR PNH** - *see Anemia I and III*

**B. MYELODYSPLASTIC SYNDROME (MDS)**

1. Definition: a chronic anemia with trilineage maturation defects and ineffective erythropoiesis
2. Incidence: several thousand cases per year in USA.
3. Pathogenesis: may follow an historical episode of aplastic anemia

4. Diagnosis: made by exclusion of other causes of anemia  
BM: abnormal megakaryocytes and RBC precursors  
 excessive ringed sideroblasts stem cells with multiple karyotypic abnormalities  
PB: pancytopenia with hypochromic anemia
5. Prognosis: in up to 40% of cases, an abnormal stem cell clone evolves into acute myelocytic leukemia (AML).

### C. MYELOPROLIFERATIVE DISORDERS

These are clonal proliferations of trilineage myeloid stem cells which may give rise to excessive numbers of erythroblastic, granulocytic, or megakaryocytic precursors. These disorders may remain clinically benign for many years, but all carry a high risk of evolution into myelocytic leukemia.

### TWO EXAMPLES OF MYELOPROLIFERATIVE DISORDERS

#### **POLYCYTHEMIA VERA (PCV) = primary polycythemia or *Polycythemia rubra vera***

- A. Definition: autonomous trilineage clone produces RBC's, granulocytes & platelets there is a real increase of RBC mass
- B. Incidence: 1/100,000 , 55-60 y/o, occasional young adult
- C. Risk factors: unknown
- D. Pathogenesis: hypersensitivity of stem cells to growth factor(s)
- E. Lab data

	<u>Males</u>	<u>Females</u>
Hb	> 18 gm/dl	> 16 gm/dl
HCT	> 55%	> 50%

- BM: proliferation of maturing erythroid and myeloid precursors causes a panhyperplasia
- PB: nucleated RBC's (> 2 per 100 WBC's)  
 leukocytosis, basophils - *produce excess histamine*  
 thrombocytosis - but platelets are *dysfunctional*

#### F. Key pathophysiology :

1. Increased blood volume - hypertension, splenomegaly
2. vascular distention - headache, dizziness

3. excess histamine - pruritus, gastritis

4. dysfunctional platelets - defective hemostasis, epistaxis

**G.** Complications: due to blood hyperviscosity and thrombosis, 30 % of patients suffer stroke or myocardial infarction catabolism of nucleated RBCs increases purine and leads to 2E gout, urate precipitates damage kidneys peptic ulcer in 20% of patients due to excess histamine secretion

**H.** Prognosis: patients may develop myelofibrosis or progress to a myelocytic leukemia

**I.** Comparison to physiologic polycythemia

1. Relative polycythemia: *RBC production is normal* hemoconcentration is caused by severe dehydration, extensive burns, or diuretic overdose

2. Secondary polycythemia: production of EPO or an abnormal EPO-like substance stimulates a true increase of RBC mass. Causes:

- hypoxemia (cardiopulmonary, environmental)
- impaired renal perfusion (local hypoxemia)
- paraneoplastic secretion of EPO-like substance

### Differential diagnosis secondary vs. P. vera

Lab Test	Secondary polycythemia	P.Vera
Arterial O <sub>2</sub>	may be low	
EPO	increased	
LAP		increased
<b>Morphology</b>		
Bone Marrow	erythroid hyperplasia	pan-hyperplasia
Immature RBC's		occasional
Platelets		increase
Basophils		increase

### MYELOFIBROSIS WITH MYELOID METAPLASIA

**A.** Definition: a proliferation of myeloid stem cells and megakaryocytes in the BM.

**B.** Incidence: uncommon / patients usually > 60 y/o

**C.** Pathophysiology / Physical Findings:

1. extramedullary hematopoiesis: massive spleen (up to 4 kg)

2. functionally defective platelets: capillary bleeding, purpura

**D. Hematology**

**BM:** megakaryocytosis, BM aspiration "*dry tap*" due to fibrosis

**PB:** replacement anemia (normocytic), giant platelets  
extramedullary hematopoiesis:

aniso/poikilocytosis - teardrop RBC's  
leuko-erythroblastosis

**E. Pathogenesis:** megakaryocytes / platelets release TGF-beta or PDGF which stimulate myelofibrosis and secondary osteosclerosis.

Some cases in Hiroshima after A-bomb

**F. Prognosis:** ~ 5 yr median survival, death due to BM failure, infections;  
acute myelogenous leukemia (AML) in 20%

## **II. MYELOCYTIC (= MYELOGENOUS, = NON-LYMPHOCYTIC) LEUKEMIAS**

LEUK-EMIA = white-blood. Originally described the increased buffy coat of centrifuged PB with an excess of neoplastic leukocytes

DEFINITION= a persistent proliferation of abnormal stem cell clone ö cells of granulocytic or monocytic phenotypes

**A. Chronic myelogenous leukemia** - abnormal stem cells can differentiate and *simulates* the full spectrum of granulocytic maturation.

Patients may survive for several years with supportive treatment

**B. Acute myelocytic leukemia** - differentiation of abnormal cells is arrested  
predominance of myeloblasts or early myelocytes

Survival without treatment is only about one year

## **III. RISK FACTORS IN MYELOCYTIC LEUKEMIAS**

**A. Occupational:** exposure to excessive total body radiation

chronic exposure to benzene, other petrochemical derivatives,  
insecticides (organophosphates)

**B. Iatrogenic:** due to chemotherapy with alkylating agents or high dose  
field radiation ca. 0.5% of patients treated for Hodgkin's disease,

0.1% of patients treated for ovarian cancer, 8 leukemias per yr for every 10,000 patients treated for breast cancer

C. Genetic: trisomy 21 = 15 X increased risk of acute leukemia

#### IV. CHRONIC MYELOGENOUS LEUKEMIA = CML

A. Incidence: 15% of adult leukemias; median age 45-55 y/o  
only 10-30% of patients > 60 y/o

B. Presentation: fatigue, weight loss, abdominal fullness,  
bleeding or easy bruising

C. Hematologic Findings:

1. **BM:** myeloid and megakaryocytic hyperplasia, M:E ratio as high as 20:1, no more than 10% promyelocytes / myeloblasts  
this is a clonal replacement of the normal trilineage stem cells. *Late stage granulocytes appear mature, but **in-situ probe shows BCR-cABL gene fusion in all cells***

2. **PB:** moderate anemia, WBC 100,000-500,000/mm  
granulocytes in progressive stages of maturation:  
abnormal myelocytes, basophils, eosinophils

decreased LAP in neutrophils = failed biosynthesis of this bactericidal enzyme helps to R/O a benign leukemoid reaction

D. Organ Pathology: massive splenomegaly ( > 5 kg) due to leukemic cell infiltration

E. Molecular Genetics:

BCR-cABL: fusion of the cABL protooncogene from chromosome 9 with the BCR gene in the bcr region of chromosome 22  
truncation of chromosome 22 (large Robbins Fig. 8-28) = **Ph<sup>1</sup>** detected by Southern blot or PCR abnormal mRNA transcripts detected by RT-PCR and Northern blot.  
The chimeric protein = p210<sup>BCR-ABL</sup> can be detected by Western blot. Antibodies are directed against N-terminal region of BCR, C-terminal region of ABL

F. Pathogenetic Mechanism: ABL proteins are tyrosine kinases which regulate cell growth. The chimera BCR-ABL is overactive. It increases cell sensitivity to growth factors and suppresses apoptosis.

Transfection of *BCR-cABL* into mice produces a leukemia which can be suppressed by antisense oligodeoxynucleotides or antibody to the chimeric protein. In humans, *BCR-ABL* translocations may occur sporadically. Leukemogenesis depends upon an unknown trigger.

**G. Pathophysiology:** stem cell proliferative activity is increased.

CML cells have defective cytoadhesion and are released prematurely from the BM. Thus the PB granulocyte pool 10-100 X (see *Robbins Fig. 15-2*) while the cell half-life 85-10 X

**H. Prognosis:** Patients can respond to Imatinib mesylate (Gleevec), a small organic compound that blocks the ATP binding site of tyrosine kinases. After a 3-5 yr chronic phase, 2/3 cases evolve to acute myelocytic leukemia (AML) 1/3 evolve to a B-cell acute leukemia (ALL). This indicates the clonal origin from a pluripotent stem cell. Death is due to BM failure: opportunistic infections or bleeding complications