

## MYELOID LEUKEMIA TEACHING POINTS

### Epidemiology

1. Leukemia accounts for ~31% of all childhood cancer occurring before age 15 years and about 25% of that which occurs before 20 years of age
2. About 3250 cases of leukemia/yr in US before age 20
3. Acute myelogenous leukemia (AML) comprises about 20%, chronic myelogenous leukemia (CML) comprises about 3% of childhood leukemia cases. Other rare myeloid leukemias account for 1-2% of cases.
4. AML incidence peaks in first 2 years of life, declines to a nadir at 9 years and increases slowly thereafter during the adolescent years.
5. CML is rare in early childhood, then begins to increase in incidence in mid adolescence
6. Juvenile myelomonocytic leukemia (JMML), previously termed juvenile chronic myelogenous leukemia (JCML), is a rare disorder that occurs almost exclusively before 2 years of age.
7. Incidence of AML has been stable over past 20 years in US, with the exception of perhaps an increase in cases diagnosed before one year of age.
8. Little is known about the causes of myeloid leukemias, but there appears to be little role of classic genetic predisposition, lifestyle factors such as diet or environmental exposures such as electric power lines
9. Children with Down syndrome have a markedly increased risk of AML (10-20 fold increase), particularly acute megakaryocytic leukemia (M7 AML; see below) that occurs in the first 2 years of life. AML in DS is more responsive than that which occurs in children without DS and is generally treated less intensively.
10. Children with DS also can develop transient abnormal myelopoiesis in the first month of life that looks like M7 AML, but usually resolves spontaneously.

### **AML**

#### Presenting Symptoms

1. Major symptoms are those caused by bone marrow failure due to replacement of normal marrow elements with leukemia cells: pallor and fatigue (anemia); bruising, petechiae and bleeding (thrombocytopenia); and infection (neutropenia).
2. Coagulopathy is more common in AML than in ALL, and is particularly common in those with acute promyelocytic leukemia (APML or M3 AML; see below)
3. Extramedullary disease can also occur in AML, sometimes manifesting itself as tumor masses termed granulocytic sarcomas or chloromas. These are especially common in monocytic subtypes of AML (M4 and M5; see below)
4. Bone pain (general irritability in younger children) is common due to expansion of the marrow cavity
5. Fever is relatively common and is usually not due to infection and often resolves within days of beginning therapy
6. About 5% of patients have CNS involvement at diagnosis, which is most often asymptomatic. However, can have symptoms due to CSF pleocytosis (headache, neck stiffness, irritability, vomiting) and/or signs of increased intracranial pressure. Cranial nerve palsies are occasionally observed.
7. Patients with AML who have very elevated white blood cell counts (>100-200,000) may exhibit signs due to hyperleukocytosis that can include hypoxemia due to pulmonary "sludging" and stroke-like CNS symptoms.

### Diagnosis and initial evaluation

1. Differential diagnosis includes non-malignant (JRA, mononucleosis or other viral infection, ITP, pertussis/parapertussis, aplastic anemia) and malignant (lymphoma, small round blue cell tumors such as neuroblastoma, Ewing's sarcoma, etc.) disorders
2. Initial evaluation should include a careful history and PE that specifically addresses areas outlined above.
3. Laboratory evaluation should include tests needed to establish the diagnosis and define the extent of involvement: CBC with review of peripheral smear, bone marrow aspirate +/- biopsy (morphology, immunophenotype, cytogenetics, molecular genetics), LP, Chest Xray to exclude mediastinal mass (must do prior to any general anesthesia!).
4. In addition, need to define other problems that may be present including screens for metabolic abnormalities: lytes, BUN, Cr, Ca, Mg, Phos, uric acid.
5. If febrile, culture and treat empirically with broad spectrum IV antibiotics

### Detailed characterization of leukemia

1. Bone marrow morphology: AML blasts are typically larger than those seen in ALL and have cytoplasmic granules. Cytochemical stains show +myeloperoxidase; monocytic forms can express non-specific esterase (NSE). Auer rods (needle like azurophilic granules) are diagnostic of AML
2. Leukemias must be characterized by flow cytometry to define the pattern of surface and cytoplasmic antigen expression. AML cells typically express myeloid associated antigens (CD13, CD14, CD33). Some cases may also express lymphoid antigens, especially T-cell antigens such as CD7.
3. AML cases are subclassified by the FAB (French-American-British) classification system into subtypes M0-M7. M0 is minimally differentiated, M1 and M2 displayed increased granulocytic differentiation. M3 is APLM and exhibits arrest at the promyelocyte stage of differentiation. M4 and M5 display more monocytic features, M6 is erythroid leukemia and M7 is acute megakaryocytic leukemia.
4. Cytogenetics are performed to identify common non-random abnormalities that may have prognostic significance. Some of these abnormalities can also be identified by specific molecular screening tests.

### Genetics of AML

1. At least 75-80% of AMLs have identified cytogenetic abnormalities. These reflect underlying genetic changes involved in disease pathogenesis. They are somatic mutations, not germline defects so they are not present in normal cells and disappear when remission is achieved.
2. Non-random chromosome translocations (exchanges of genetic material between chromosomes) are common in AML and define specific subtypes of disease. These commonly create fusion genes and proteins. Major subcategories include the abnormalities that affect the core binding protein family: t(8;21) and AML1-ETO and inv(16) and CBF $\beta$ -SMMHC.
3. APLM is a clinically distinct subtype of AML characterized by the t(15;17) that produces PML-RAR $\alpha$  fusion. It is treated differently from other subtypes of AML (see below)
4. Chromosome deletions also occur in AML; the most common are cases with monosomy 7 or deletions of all or part of chromosome 5. These subtypes are often associated with a myelodysplastic (MDS) phase and are often refractory to chemotherapy.

### Prognostic Factors

1. Adverse: high WBC (>100,000; less important in children), antecedent MDS or secondary AML induced by chemotherapy treatment, monosomy7, complex cytogenetic abnormalities
2. Favorable: t(8;21), inv(16), t(15;17)

### Treatment

1. As recently as the early 1970s, childhood AML was largely incurable. Since then cure rates have steadily improved such that 40-50% of children with AML are cured today
2. Therapy for AML is much more intensive, but shorter (lasting 6-9 months) than ALL therapy, involving repeated cycles of aggressive chemotherapy that generally lead to marrow aplasia and substantial risks of infection. Treatment is largely inpatient and infectious complications are a major issue. Toxic death rates for AML therapy are still 5-10%.
3. Most US groups consider matched sibling stem cell transplant to be the therapy of choice for AML.
4. Major active agents include the anthracyclines (Daunomycin, Doxorubicin, Mitoxantrone) and Ara C, given either at conventional or high (HiDAC) doses.
5. APLM1 is caused by the 15;17 translocation that produces a retinoic acid receptor alpha fusion protein, PML-RAR $\alpha$ .  $\square\square\square\square$  blocks myeloid differentiation.  $\square\square\square\square$  acologic doses of retinoic acid overcome this differentiation block and allow cells to differentiate terminally and die. Retinoic acid is now a standard component of all APLM1 treatment regimens, and has revolutionized treatment of this subtype of AML.
6. Other new "targeted" therapies under study include myelotarg, in which the potent but highly toxic chemotherapy agent calicheamicin is conjugated to an anti-CD33 monoclonal antibody. This is internalized into CD33+ cells and the chemotherapy agent is released intracellularly.
7. If relapse occurs, chance of salvage depends on various factors. One of strongest is the time of relapse following initial diagnosis (the sooner one relapses, the lower the chance of salvage). Relapse regimens almost always include stem cell transplantation.

## **CML**

### Presenting Symptoms

1. Patients usually have non-specific complaints and are not toxic. They may have fatigue from anemia, bone pain or abdominal symptoms due to massive splenomegaly
2. Laboratory evaluation typically shows a markedly elevated WBC (usually 100,000+) and platelet count (usually 500,000+, often >1,000,000) with all mature elements and few blasts
3. Exam is usually notable for splenomegaly, often massive
4. Some patients exhibit symptoms due to hyperleukocytosis (see above)

### Diagnosis and initial evaluation

1. Clinical picture and blood counts are often pathognomonic
2. Disease is tri-phasic with indolent chronic phase (CP) characterized by marked expansion of myeloid cells. Average length of chronic phase is 3 years, but can go over 20 years.
3. Patients inexorably transform (15-20%/yr) into a "blast crises" that is indistinguishable from AML (75-80%) or ALL (20-25%) and is often refractory to chemotherapy
4. A transition state, termed the accelerated phase, is seen in some patients.
5. Initial evaluation must make diagnosis and define stage of disease (vast majority present in CP)

### Genetics of CML

1. CML is caused by t(9;22) or Philadelphia chromosome, which creates BCR-ABL fusion protein. All patients must have cytogenetic studies, preferably of bone marrow, to identify the Philadelphia chromosome.
2. Patients in CP have no other cytogenetic abnormalities and presence of other clonal cytogenetic abnormalities is generally considered indicative of accelerated phase
3. BCR-ABL mRNA can be detected by RT-PCR, and the fusion gene can be identified via fluorescence in situ hybridization (FISH)

### Treatment

1. CML is not cured by standard ALL or AML regimens and these generally do not eradicate the Philadelphia chromosome.
2. Disease can be readily controlled by Hydroxyurea, an oral chemotherapy agent with minimal side effects, but HU does not change the natural history of the disease
3. Stem cell transplantation is curative. Cure rates in children are 80-90% for those with an HLA-identical sibling donor and 50-70% for those with a suitable matched unrelated donor.
4. Treatment of CML has been revolutionized by the recent development of Imatinib mesylate (Gleevec), a potent oral inhibitor of the tyrosine kinase activity of BCR-ABL protein.
5. Gleevec induces rapid hematologic remissions in >95% of patients with CML in CP and most have complete or partial disappearance of Philadelphia chromosome and enter "cytogenetic remission". This never occurs with HU.
6. Most (>90%) patients who attain cytogenetic CR are still in CR 2 years later, but long term efficacy of Gleevec is unknown at that time. Resistance can develop and is often due to acquired mutations in BCR-ABL that prevent binding by Gleevec, or to amplification of BCR-ABL.
7. Role of SCT in the Gleevec era is controversial.

### **SUGGESTED READING**

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