Acute Leukemia for the Internist

Acute Myeloid/Myelogenous Leukemia (AML)

1. Epidemiology
    a. Estimates for 2011 in USA: 13,000 new cases and 9,100 deaths
    b. Incidence = 3.5 per 100,000
    c. Median age at diagnosis: 67 years
2. Presentation
    a. History:
        i. Constitutional symptoms: weight loss, night sweats, fever
        ii. Fatigue due to anemia
        iii. Bleeding due to thrombocytopenia (DIC more common with APL)
        iv. Fevers or infections from neutropenia
    b. Physical exam:
        i. Pallor, petechiae, and purpurae from low blood counts
        ii. Gum hypertrophy, hepatosplenomegaly from tissue infiltration of myeloid blasts (uncommon; classically with acute monocytic leukemia)
    c. CBC findings: WBC can be high or low, RBC and plt usually low (but not always)--presence of blasts on differential is a useful clue
3. Diagnosis
    a. Peripheral blood: greater than 20% of WHITE cells are myeloid blasts
        i. Auer rods when present identify myeloid blasts
    b. Bone marrow: greater than 20% of NUCLEATED cells are myeloid blasts
    c. "Myeloid sarcoma": a tumor of myeloid blasts outside the marrow (for example in the skin)
    d. FAB classification (M0, M1, etc.) is of historical interest, but some subtypes retain this classification due to certain features of presentation or treatment
        i. M3 = acute promyelocytic leukemia (APL)
        ii. M5 = acute monocytic leukemia
        iii. Flow cytometry has generally replaced cytochemistry, but may see both used
        iv. Flow cytometry markers of myeloid cells: CD13, CD34, CD38, CD117, HLA-DR
        v. Cytochemical stains for myeloid cells: myeloperoxidase (MPO), Sudan Black, non-specific esterase (NSE)
4. Prognosis
    a. Cytogenetics and fluorescence *in situ* hybridization (FISH) to define karyotype (monosomies, trisomies, translocations, inversions, deletions, etc.)
    b. Molecular studies for AML associated mutations (FLT3, NPM-1, CEBPA, c-kit)
    c. Favorable risk:

i. "Core binding factor": t(8;21), inv 16, or t(16;16)
ii. APL: t(15;17)

d. Intermediate-good risk (assume normal karyotype):
i. CEBPA mutation present
ii. NPM-1 mutation present without FLT-3 internal tandem duplication (ITD)

e. Intermediate-poor risk (assume normal karyotype):
i. NPM-1 mutation absent
ii. FLT-3 ITD present

f. Unfavorable risk (more common listed):
i. Single karyotypic abnormalities: monosomy 5, monosomy 7, del 5q
ii. Multiple karyotypic abnormalities:
1. "Complex karyotype": 3 or more abnormalities
2. "Monosomal karyotype": two autosomal monosomies, or one autosomal monosomy PLUS another structural abnormality
iii. Historical/morphologic details:
1. Prior chemotherapy--"treatment-related AML"
2. Prior hematologic disorder (e.g., myelodysplastic syndrome, myeloproliferative neoplasm)--"secondary AML"

5. Treatment
a. When possible, guided by prognostic information
i. Favorable prognosis: Chemotherapy Alone
ii. Non-favorable prognosis: Chemotherapy followed by Allogeneic Transplantation

b. Standard first-line option:
i. Induction: "7+3" (cytarabine for 7 days, anthracycline for 3 days)
1. Goal: remission (<5% blasts in marrow AND recovery of blood counts)
ii. Consolidation: 3 monthly cycles of cytarabine
1. Goal = maintain remission (hopefully long-term)
iii. Outcomes with this approach:
1. Favorable risk: >70% long-term remissions (?cure)
2. Unfavorable risk: <20% long-term remissions

c. Second-line options: MEC, FLAG, or other standard options vs. clinical trial

d. Special circumstances
i. Unfavorable risk: may offer clinic trial first given poor track record of 7+3
ii. Acute promyelocytic leukemia: all-trans retinoic acid (ATRA) included
1. t(15;17) creates an "oncogenic" version of RAR-alpha, a retinoic acid receptor and ATRA blocks activity of this protein and induces differentiation of leukemic blasts

Acute Lymphoid/Lymphocytic/Lymphoblastic Leukemia (ALL)

1. Epidemiology
    a. Estimates for 2011 in USA: 5,700 new cases and 1,400 deaths
    b. Incidence: 1.7 per 100,000
    c. Median age at diagnosis: 13 years (bimodal presentation)
2. Presentation
    a. History: similar to AML
    b. Examination:
        i. Pallor, petechiae, and purpurae from low blood counts
        ii. Lymphadenopathy and/or hepatosplenomegaly more common than AML
        iii. Mediastinal mass--think T-cell ALL
    c. CBC findings: same as above
3. Diagnosis
    a. Greater than 20% lymphoid blast in blood or bone marrow,
    b. FAB classification (L1, L2, or L3) rarely used
    c. Leukemic blasts may be of either B- or T-cell origin
    d. Flow cytometry has generally replaced cytochemical staining here, also
        i. Flow cytometry markers of lymphoid cells include:
            1. B-cell: CD10, CD19, TdT
            2. T-cell: CD3, CD4, CD7, CD8
        ii. Terminal deoxynucleotidyl transferase (TdT): cytochemical stain occasionally used to identify lymphoid blasts
    e. Higher risk of CNS involvement that AML--lumbar puncture for all
    f. Testicular involvement also possible in males--ultrasound if symptoms
4. Prognosis
    a. High-risk features:
        i. Age > 30
        ii. Elevated WBC: >30k for B-cell, >100k for T-cell
        iii. Cytogenetics:
            1. t(9;22): a.k.a., Philadelphia chromosome, arguably most important
            2. Others: t(4;11), t(8;14), complex karyotype
    b. ALL in the elderly (i.e., over age 60) has a particularly poor prognosis: <10% long-term remission
5. Treatment
    a. Generally more complicated than AML
        i. Most regimens with multiple phases that can span 2 years
        ii. Usually include many different agents

iii. Common agents: anthracycline, cyclophosphamide, methotrexate, vinca alkaloid, steroid
iv. All similarly effective at inducing remission (about 80-90%)

b. CNS prophylaxis/treatment
    i. Blood-brain barrier makes this a potential "sanctuary site"
    ii. Administration of intrathecal chemotherapy with initial diagnostic LP
    iii. If CSF negative, include additional prophylaxis throughout treatment
    iv. If positive, active treatment of CNS is more intense
        1. More frequent dosing--surgical placement of reservoir
        2. Sometimes include craniospinal irradiation
c. Testicular irradiation if involvement suspected
d. Controversy over best treatment of young adults
    i. Pediatric protocols slightly different (more intense)
    ii. Outcomes may be better with these protocols than with adult protocols
e. Special circumstances
    i. ALL associated with t(9;22): include oral tyrosine kinase inhibitor (e.g., imatinib, dasatinib)
    ii. Elderly: treatment with multi-drug regimens usually not possible due to toxicity concerns

<u>Suggested Additional Reading</u>

1. Howlader N, *et al*. (eds). *SEER Cancer Statistics Review, 1975-2008*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.
2. Vardiman JW, *et al*. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood.* 2009 Jul 30;114(5):937-51.
3. Estey E, Dohner H. Acute myeloid leukaemia. *Lancet*. 2006 Nov 25;368(9550):1894-907.
4. Rowe JM, Goldstone AH. How I treat acute lymphocytic leukemia in adults. *Blood*. 2007 Oct 1;110(7):2268-75.
5. Many topics on *UpToDate*.