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. "Monosom al 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

Suggested Additional Reading
5. Many topics on UpToDate.