Acute Leukemia in the Adult: Current and Evolving Approaches to Diagnosis and Management

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Advances in the Treatment of Acute Leukemia

- Transfusion support
- New antimicrobials
- New chemotherapeutic agents
- Advances in high dose therapy with autologous or allogeneic transplantation

Overview of Acute Leukemia

- Leukemias are clonal, neoplastic proliferations of immature cells of the hematopoietic system, which are characterized by aberrant or arrested differentiation
- Accumulate in the bone marrow, and replace normal hematopoietic cells
- Circulate in the blood and may infiltrate other tissues (skin, gingiva, spleen, testes, central nervous system)
- Classic signs and symptoms are the result of bone marrow failure (neutropenia, anemia, thrombocytopenia), and from resultant hemorrhage, infection and anemia
- Acute leukemias can be broadly grouped based on phenotype and genotype into:
  - Myelogenous
  - Lymphoblastic

Epidemiology of Acute Leukemias

- Incidence of leukemia is approximately 3% of all cancers, or approximately 15,000 new cases each year
- Approximately 4000 new cases of acute lymphoblastic leukemia, and about 11,000 new cases of acute myelogenous leukemia
- ALL has a bimodal distribution with peak occurrences in adolescence and again after age 70.
- Median age of onset for adult AML is 60-65 years

Etiology

- Cause is generally unknown
- History of prior chemotherapy (especially carboplatin, etoposide, procarbazine, cyclophosphamide, CCNU) and radiation therapy increases risk
- Environmental/occupational exposures – ionizing radiation, cigarette smoking (20% AML), benzene
- Increased risk of leukemia with Down syndrome, Fanconi’s anemia, Bloom’s syndrome, or ataxia-telangiectasia

Presentation
- Fatigue over 1 to 3 months
- Bone marrow failure
- Hemorrhage
- Infection / fever
- Easy bruising
- Minimal to moderate weight loss
- Bone pain
- Hepatic/splenic enlargement

Classification of Acute Leukemias
- Three questions must be answered to diagnose and classify an acute leukemia
  - What is the lineage?
  - What is the maturational stage?
  - What is the genotype?

Bone Marrow Aspirate and Biopsy and Peripheral Blood Smear
- Evaluation of the morphology (microscopic appearance of the leukemic cells)
- Provides tissue for immunohistochemical stains to identify the lineage of the cell (eg. lymphoid or myeloid)
- Provides material for flow cytometry to determine the percentage of high immature cells, and the pattern of expression of cell surface or cytoplasmic markers (eg. CD 20, TdT, CD 33, CD 34, HLA-DR)
- Provides tissue for molecular diagnostics [cytogenetics, RT-PCR, FISH] to determine if there is a chromosomal abnormality (eg. Philadelphia chromosome in ALL) or translocation [eg. t (15;17), t (8;21), inv (16)]

Morphology
- Morphologic examination is performed to establish the lineage
  - Peripheral smear
  - Bone marrow aspirate
  - Bone marrow biopsy
  - Tissue analysis (eg. lymph node, CSF)

Cytochemistry and Immunophenotyping
- Cell Surface Antigen Testing
  - Immunofluorescence – flow cytometry blood and bone marrow aspirate
  - Immunoperoxidase – tissue or bone marrow biopsy
- Cytoplasmic and nuclear antigen testing
  - Cytoplasmic immunoglobulin
  - TdT (Terminal deoxynucleotidyl transferase)
- Flow Cytometry – provides quantitative values of immunofluorescence per cell

Cytogenetics/Molecular Diagnostics
- Cytogenetics are molecular diagnostic studies which detect genetic rearrangement or deletion of a gene.
- Metaphase cytogenetics
- RT-PCR – reverse transcriptase polymerase chain reaction
- PCR- polymerase chain reaction
- FISH – fluorescence in situ hybridization
**French – American – British (FAB) Group**

- Acute myeloid leukemia has been divided into 8 FAB subtypes M0-M7.
- Acute Lymphoid Leukemia has been classified into 3 FAB subtypes L1-L3.

**Acute Leukemia**

**Acute Myelogenous Leukemia**
- M0 Undifferentiated
- M1 Myeloblastic
- M2 Myeloblastic
- M3 Promyelocytic
- M4 Myelomonocytic
- M5 Monocytic
- M6 Erythroleukemia
- M7 Megakaryoblastic

**Acute Lymphocytic Leukemia**
- L1 Childhood (pre B- and T-cell)
- L2 Adult (pre B- and T-cell)
- L3 Burkitt’s type (B-cell)

**Prognostic Features ANLL**

<table>
<thead>
<tr>
<th>Age</th>
<th>+&lt;45</th>
<th>-&gt;60 (&lt;2)</th>
<th>Involvement</th>
<th>Antecedent</th>
<th>myelodysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>de novo</td>
<td>Antecedent</td>
<td>myelodysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FISH</td>
<td>WBC</td>
<td>N2 (&gt;-5,000/mm3)</td>
<td>Dec ~&gt;100,000/mm3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphology</td>
<td>Auer rods, M1 - 4</td>
<td>M0, M6, M7</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Markers</td>
<td>Lymphoid markers (CD34+, mdr-1+)</td>
<td>CD2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytoreduction - CR</td>
<td>Rapid</td>
<td>Delayed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics - most potent correlate</td>
<td>8;21, 11;16, 15;17</td>
<td>5;del(7q), 5;del(5q), 11q23, 3p21, 3q26, complex</td>
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**Adverse Prognostic Factors in Adult ALL**

<table>
<thead>
<tr>
<th>Remission Induction</th>
<th>Remission Duration / Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Age &gt; 35 years</td>
</tr>
<tr>
<td>WBC &gt; 30,000</td>
<td>WBC &gt; 30,000</td>
</tr>
<tr>
<td>Non-T cell phenotype</td>
<td>Non-T cell phenotype</td>
</tr>
<tr>
<td>Lack of mediastinal adenopathy</td>
<td>t(9;22) or BCR/ABL rearrangement</td>
</tr>
<tr>
<td>Poor performance status</td>
<td>t(4;11) and variants</td>
</tr>
<tr>
<td>Burkitt cell (L3)</td>
<td>Burkitt cell (L3)</td>
</tr>
<tr>
<td>Phenotype (Sig+)</td>
<td>Phenotype (Sig+)</td>
</tr>
</tbody>
</table>

**Evaluation of Minimal Residual Disease**

- Morphology
- Bone Marrow Aspirate and Biopsy
- FISH for specific translocations
- Peripheral blood smear
- Flow cytometry
- Southern blot
- Polymerase chain reaction

**Initial Evaluation of the Patient with Acute Leukemia**

- Physical examination and family history
- Dental evaluation
- Viral serologies, including HSV, CMV, hepatitis, and HIV
- Cardiac status evaluated with MUGA or echocardiogram
- Leukapheresis if WBC > 100,000 or symptomatic
- Coagulation screening
- Establish Central Venous Access
- HLA typing
- Sperm banking
**Concepts and Definitions**

- **Induction Therapy**
  - Goal: rapid clearing of leukemic cells from peripheral blood with subsequent marrow aplasia

- **Post Remission Therapy**
  - Goal: prolong the duration of remission

**Sample Induction Regimen-AML**

- Cytarabine 100-200 mg/m²/day by continuous IV infusion Days 1-7
- Daunorubicin 45 mg/m²/day Days 1-3
- Idarubicin 12 mg/m²/day Days 1-3
- Mitoxantrone 12 mg/m²/day Days 1-3

**Sample Induction Regimen-HIDAC**

- Cytarabine 1-3 gm/m² IV over 2-3 hours every 12 hours x 12 doses days 1-6
- Daunorubicin 45 mg/m²/day Days 1-3
- Idarubicin 12 mg/m²/day Days 1-3
- Mitoxantrone 12 mg/m²/day Days 1-3

**Acute Myelogenous Leukemia**

**Rationale for Intensive Post-Remission Therapy**

- Even with CR, estimated that 10 billion leukemia cells remain.
- Some form of therapy required to prevent disease relapse
- Stratify based on age and cytogenetic features

**Options for Post-Remission Therapy-AML**

- 60 years old, CR to induction, with good risk cytogenetic abnormalities
- Consolidation with 4 cycles of high dose cytarabine (3 gm/m²) followed by 4 cycles of maintenance with cytarabine and daunorubicin
- Alternative: 1-2 cycles of high dose cytarabine followed by autologous transplantation or matched related transplantation
Options for Post Remission Therapy-AML

- < 60 years old, CR to induction with intermediate risk or high risk cytogenetics
  - Consolidate with:
    - 1-2 cycles of high dose cytarabine, and proceed to autologous or allogeneic transplantation
    - or
    - 4 cycles of high dose cytarabine
- > 60 years
  - Enroll in clinical trial if available
  - If not available, consolidate with: 2 cycles of standard dose cytarabine 100 mg/m² + anthracycline (Idarubicin, Daunorubicin or Mitoxantrone)

Management of Primary Induction Failure/Refractory Disease-AML

- < 60 years old with a related or unrelated donor?
  - Related or unrelated allogeneic transplantation
- < 60 years old without a related or unrelated donor
  - Clinical trial, monoclonal antibody therapy
- > 60 years old?
  - Clinical trial, monoclonal antibody therapy (Mylotarg®) or supportive care

Salvage Therapy for Disease Relapse- AML

- Early relapse with low tumor burden and identified donor?
  - Allogeneic transplantation
- Early relapse, but no donor?
  - Clinical trial
- Relapse after long remission?
  - Reinduction using original agents or clinical trial, followed by autologous or allogeneic transplantation

Therapy of Acute Lymphoblastic Leukemia

- Remission Induction
- CNS Prophylaxis
- Consolidation and Intensification
- Maintenance

Therapy of Acute Lymphoblastic Leukemia

- Remission Induction
- CNS Prophylaxis
- Consolidation and Intensification
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- 3-4 drug regimen given on monthly cycle for 2 years
- Vincristine (IV) Prednisone (PO)
- Methotrexate (PO)
- 6-Mercaptopurine (PO)

Remission Induction-ALL

- Vincristine and prednisone serve as backbone of induction regimen + 2 or more additional agents
- Examples of other agents added to regimen: daunorubicin, doxorubicin, idarubicin, L-asparaginase, cyclophosphamide, cytarabine, methotrexate, 6-mercaptopurine, 6-thioguanine
Central Nervous System Prophylaxis

- Without CNS prophylaxis, between 10-50% of patients will develop CNS relapse.
- Craniospinal irradiation of 18-24 Gy combined with intrathecal methotrexate is the standard.
- More aggressive systemic chemotherapy also contributes to a reduced risk of CNS relapse.

Intensification-Consolidation-ALL

- Intensification-consolidation usually requires the use of increased doses of drugs used in induction, or the addition of non-cross-resistant new agents.
- May be given early (for example 1 month after induction) and/or late (for example 5 months after induction).
- Allogeneic and autologous PBSCT have important roles for those with high risk features, who are younger and have a donor.

Maintenance Therapy-ALL

- Typically, daily 6-Mercaptopurine (po) and weekly methotrexate (IV) for 18 to 36 months.
- Vincristine and prednisone pulses.
- Optimal drugs, doses and duration have not been determined.

Refractory or Relapsed ALL

- Significance and management of relapse influenced by:
  - Duration of first remission
  - Intensity of initial regimen used
  - Site of relapse

Relapsed ALL

- Relapse on therapy or shortly after completion?
  - Reinduce with drugs not previously received
  - Give CNS directed therapy
  - Consider consolidation and intensification to prolong duration of 2nd remission
  - Best hope for long term survival is allogeneic transplant. Autologous transplant with cells collected during second remission.

Relapsed ALL

- Isolated extramedullary relapse in CNS?
  - Additional systemic therapy + transplant
- Isolated testicular relapse?
  - Additional systemic therapy including CNS prophylaxis and testicular XRT
- Late relapse?
  - Reinduce with vincristine, prednisone, asparaginase and an anthracycline + transplant.
**Therapy of Acute Promyelocytic Leukemia**

- **Remission Induction Therapy**
  - Daunorubicin + All-transretinoic Acid (ATRA) +/- Ara-C
- **Consolidation with 3 courses of Ara-C and Anthracycline**
- **Maintenance**
  - Vincristine
  - Oral maintenance therapy with 6-Mercaptopurine and ATRA

- **Relapse**
  - Arsenic trioxide
  - Reinduction with Anthracycline, Cytarabine and ATRA
  - Proceed with autologous PBSCT (if PCR negative for PML-RAR), allogeneic transplantation or clinical trial

**Patient Monitoring During Therapy**

- CBC, relevant chemistries (eg LFTs, tumor lysis labs, BUN/Cr)
- Bone marrow aspirate and biopsy
  - 14 days after treatment initiation, and every 7-14 days thereafter until evidence of normal hematopoiesis or persistent leukemia documented
- Evaluate with cytogenetics (if there is an abnormality) or other method to detect minimal residual disease (MRD) eg. Polymerase Chain Reaction (PCR), Fluorescent Insitu Hybridization (FISH)
- History and physical

**Response Criteria in Acute Leukemia**

- **Complete Response**
  - Absolute neutrophil count 1500/microliter
  - Platelets 100,000/microliter
  - No leukemic blasts in peripheral blood
  - No extramedullary organ involvement
  - <5% blasts in bone marrow, and cellularity <20%
  - 15% normal erythropoiesis
  - >25% granulopoiesis

- **Partial Response**
  - 6-25% blasts in bone marrow
  - >10% normal erythropoiesis
  - >25% normal granulopoiesis

**Supportive Care of the Patient Undergoing Treatment of an Acute Leukemia**
Supportive Care of the Patient Undergoing Treatment of an Acute Leukemia

- Hydration
- Allopurinol
- Prophylactic Antimicrobials
- Steroid eye gts for HIDAC
- Cytokine Support
- Blood Products- Irradiated and filtered
- Menses suppression

Leukemia and Lymphoma Society
American Cancer Society
NCI Cancer Information Service
National Marrow Donor Program

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Treatment of Acute Leukemia in the Adult

New Strategies- New Targets

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New Agents for the Treatment of Leukemia

- Cytotoxic Agents
  - Triarabinine, Clofarabine
  - Arizona, Treosulfan (Trexenen)
- Monoclonal Antibody Therapies
  - Engineered antibodies that bind to cell surface antigens on malignant cells
  - Conjugated with cytotoxic molecules
  - Deliver targeted cytotoxicity to leukemic cells
- Monoclonal antibody therapies include antibodies targeting CD33 (MylotargR), CD52 (Campath-1H), others in development
- Therapies with Novel Targets/Mechanisms of action
  - Inhibit multidrug resistance protein (MDR1/PGP)
  - Cyclosporin, PSC 854
  - Hypomethylating Agents (induce activation of tumor suppressor genes silenced by leukemia)
  - Decitabine (DAC), 5-Azacytidine
  - Promote Terminal Differentiation by Arresting Cell Cycle
  - ATRA, Topotecan (CPT-11), Bryostatin-1
  - Induce/facilitate apoptosis, inhibit cell growth signaling pathways, inhibit angiogenesis
  - PS-341, SU5416, PTK 787
**Therapies with Novel Targets**
- **Promote Apoptosis (Cell Death)**
- Arsenic trioxide

- **Angiogenesis Inhibitors**
  - Thalidomide, SU5416, PTK 787
  - Inhibition of Tyrosine Kinase (inhibits proliferation of cells containing BCR-ABL)
  - STI-571 (Gleevec™)

- Farnesyl transferase Inhibitors (blocks cell signaling pathways preventing cellular changes associated with malignant cell growth)
  - R115777

- **Promote tumor-specific T-Cell Activation**
  - Vaccine-based strategies

**Leukemia in the Elderly**
- AML- median age at diagnosis is 63 years.

- Older individual may be less able to tolerate intensive treatment

- AML appears to be biologically different in older adult
  - Cytogenetic abnormalities associated with resistant disease
  - Increased expression of the multidrug resistant marker, p-glycoprotein

- Intensifying induction or post-remission therapies are not the answer. Novel strategies and clinical trials are urgently needed

**Secondary Acute Leukemias**
- Secondary or therapy related AML accounts for 10-20% of all AMLs

- Most pts with secondary acute leukemia have an unfavorable outcome

- Prior chemotherapy with alkylating agents or topoisomerase II inhibitors such as etoposide

- Allogeneic PBSCT may be the treatment of choice, if donor is available

**Case Study**
- 46 year old Caucasian male who presented to family MD with nausea, vomiting, fevers and weight loss

- Sonogram of the abdomen shows spleen of 15.5 cm (upper limit of normal 12 cm), with some sludging in the gallbladder and fatty liver infiltration. Patient scheduled for cholecystectomy.

- Antecedent CBC done three months earlier as part of routine care showed: a WBC of 6.8, Hemoglobin of 15, and platelet count of 509,000 with a normal differential
In addition to the presence of circulating blasts, what clinical features suggest the diagnosis of ALL?

- Leukocytosis, anemia, thrombocytopenia
- Hepatosplenomegaly
- Adenopathy

What components deserve special attention during review of systems in a patient with presumed ALL?

- Symptoms associated with neutropenia, thrombocytopenia, and anemia including infections, bleeding, bruising, fatigue, pallor, tachycardia or chest pain
- Symptoms associated with hepatosplenomegaly such as nausea, vomiting, dyspepsia, abdominal pain, early satiety
- Symptoms associated with CNS involvement and/or leukostasis including headache, visual changes, weakness, syncope, dizziness

Physical Examination

Within normal limits except for:

- 1 cm right supraclavicular lymph node and 1 cm right axillary lymph node. Shotty adenopathy along the inguinal ligament that is not measurable. No other palpable adenopathy in the cervical, supraclavicular, axillary or inguinal regions
- Spleen palpable 4 cm below the left costal margin. Liver edge palpable 1 cm below the right costal margin. Abdomen non-tender.

Which of the following laboratory abnormalities might you expect to see in this patient?

- Elevated LDH
- Hyperuricemia
- Renal failure
- Hyperkalemia

What additional diagnostic studies are required to evaluate this pt?

- Bone marrow aspirate and biopsy
- CT of the head
- CT of the chest/abdomen and pelvis
- Lumbar puncture
- Lymph node biopsy

Case Study

The diagnostic work-up is complete, and the diagnosis of Philadelphia chromosome (Ph+), B-lineage ALL is confirmed.

- Phenotyping of leukemic blasts demonstrate CD 34, CD-38, CD 10, CD 20, and DR positive, but negative for CD 13 and CD-33
- Chest CT demonstrates hilar lymphadenopathy.
- Analysis of the cerebrospinal fluid reveals total protein of 59, glucose of 49, 0 white cells, 0 red cells, and negative cytology
What other components will need to be addressed/planned for as this pt begins definitive therapy for his ALL?

- HLA typing of pt and siblings
- Sperm banking
- Echocardiogram/MUGA
- Establish vascular access
- Hydration and allopurinol
- Infection prophylaxis against Pneumocystis carinii pneumonia with Bactrim 3 x/week

Case Study

The patient begins induction therapy with the following regimen:

- Cyclophosphamide 1200 mg/m² on Day 1
- Daunorubicin 45 mg/m² on Days 1, 2, 3
- L-Asparaginase 6000 units/m² on Days 5, 8, 11, 15, 18, 22
- Vincristine 2 mg IV on Days 1, 8, 15, 22
- Prednisone 60 mg/m² on Days 1-21

Which of the following urgent problems might you expect to see in this pt?

- Tumor lysis syndrome
- Leukostasis
- Disseminated intravascular coagulation
- Sepsis/Septic Shock

Case Study

- This patient’s protocol requires monthly intrathecal methotrexate prophylaxis but no cranial irradiation.
- Hospitalized for febrile neutropenia once during the past 2 months
- 25 lb weight loss, fatigued
- About to commence maintenance phase of treatment with methotrexate and 6 mercaptopurine, along with monthly intrathecal treatments x 6

How would this patient be monitored at regular intervals to determine his progress?

- CBC with differential q 2 weeks
- Bone marrow aspirate and biopsy monthly
- BUN/creatinine q 2 weeks
- CT of the chest q 2 weeks

Case Study

- Complete blood count with differential
- Bone marrow biopsy
- Cytogenetics
- Molecular diagnostics
- Bone marrow biopsy
8 months after diagnosis, routine evaluation reveals a sharp decline in the platelet count, and blasts are noted on the bone marrow aspirate and biopsy. Molecular diagnostics confirm the reappearance of the BCR – ABL abnormality.

Admitted for re-induction with M-Amsacrine and high dose Ara-C, and seen in consultation regarding possible allogeneic stem cell transplantation.

After obtaining remission with high dose cytarabine, the pt proceeds to allogeneic stem cell transplant from his 6/6 HLA antigen matched sister.

His preparative regimen for transplant included cyclophosphamide, thiotepa, total body irradiation, with a testicular boost.

Post transplant course complicated by CMV reactivation and Stage II graft versus host disease of the skin and gut.

Remission status confirmed by recent bone marrow aspirate and biopsy which demonstrates 100% donor engraftment, and the absence of the Ph chromosome and the BCR-ABL abnormality.

He is undergoing the second of six planned monthly cycles of post-transplant intrathecal chemotherapy with methotrexate.