Acute Lymphoblastic Leukemia (ALL)

Ryan Mattison, MD
University of Wisconsin
March 2, 2010
ALL Epidemiology

- 20% of new acute leukemia cases in adults
- 5200 new cases in 2007
- Most are de novo
- Therapy-related ALL
  - Topo II inhibitors
  - Alklyating agents
  - MLL rearrangements (11q23)
ALL: WHO Classification

- **Precursor B-cell**
  - TdT+, CD34+, surface Ig negative
  - CD19, CD22, CD79a positive, CD 20 variable

- **Precursor T-cell**
  - TdT+
  - CD3+, often CD2, CD4, CD8 positive

- **Mature B-cell (Burkitt)**
  - CD19, CD22+
  - Surface Ig positive
Cytogenetics

- Recurrent abnormalities seen in 60-70% of cases
- High risk
  - t(9;22), hypodiploid, 11q23 involvement
- Lower risk
  - Hyperdiploid (>46), t(12;21)(p13;q22) TEL/AML1
- Mature B cell (Burkitt’s)
  - t(8;14)-most common, t(2;8), t(8;22)
  - Which gene is at 8q24?
Workup

- CBC, CMP, LDH
- Bone marrow exam
  - Morphology
  - Flow cytometry
  - Immunohistochemistry
Prognostic Factors

- **Age** (<30, 30-60, >60)
- **WBC at diagnosis**
  - Precursor B cell (<30,000)
  - Precursor T cell (<100,000)
- **Time to achieve CR**
  - <4 weeks
- **Cytogenetics**
- **Minimal residual disease presence/absence**
Minimal Residual Disease

- **PCR- or flow-based assays**
  - PCR- 1:100,000
  - Flow- 1:1000 to 1:10000

- **PCR targets**
  - BCR-ABL in Ph+ disease
  - IgH rearrangements in precursor-B ALL
  - T-cell receptor rearrangements in precursor-T ALL

- Presence of MRD usually precedes frank relapse

- **Challenge:** Substantial variability due to different labs and techniques

- **Guidance for therapy intensity:** Ongoing studies
Therapy Strategies

- **Induction**
- **Consolidation**
  - Several phases termed “interim maintenance” and “delayed intensification”
- **Maintenance**
  - Can last for 2-3 years after the time of initial diagnosis
- **Complicated! Follow a good recipe…**
ALL Induction

- Most use 4 or 5 drugs, including
  - Vincristine
  - Steroids
  - Anthracycline
  - Cyclophosphamide
  - +/- asparaginase

- Expected remission rates of 80-90%, lower for older patients
ALL Consolidation

- Many have evolved from pediatric regimens
- Drugs include
  - Cytarabine
  - Etoposide
  - Methotrexate
  - 6-mercaptopurine
  - 6-thioguanine
UW Options

- **Hyper-CVAD** developed at MD Anderson
  - Alternating A-B, 3 weeks each, four cycles
  - A-Cyclophosphamide, vincristine, Adriamycin, dexamethasone
  - B-Methotrexate, cytarabine

- **BFM (Berlin-Frankfurt-Munster)**
  - Induction-Vincristine, daunorubicin, prednisone, asparaginase
  - Consolidation-Cyclophosphamide, 6-MP, cytarabine
  - Interim Maintenance-Oral MTX, 6-MP
  - Delayed Intensification-Similar to induction and consolidation
CNS Therapy

- Only 10% have CNS involvement at diagnosis
- Every patient needs an LP at diagnosis
- Without prophylactic therapy, 35%-75% of patients will develop CNS disease
- Risk factors for CNS involvement
  - Mature B-cell disease
  - High serum LDH
- Symptoms
  - Headache, meningismus, fever, cranial nerve palsy
CNS Prophylaxis and Therapy

- Craniospinal radiation
- Intrathecal methotrexate, cytarabine, hydrocortisone
- Systemic high dose cytarabine, methotrexate
- For symptomatic CNS disease
  - IT “triple therapy”
  - Radiation therapy: 15 to 20 Gy
Maintenance Therapy

- **Rationale:** Long exposure to antimetabolite drugs will eliminate any subclones that persist after induction/maintenance
- **Lasts 2-3 years after initial diagnosis**
- **Drugs**
  - Daily 6-MP
  - Weekly oral methotrexate
  - Monthly vincristine, steroids
  - Periodic intrathecal chemotherapy
Ph+ ALL

- t(9;22) and BCR-ABL
  - Very poor prognosis, median survival 9 months
  - p190 (ALL) vs p210 (CML)
  - Most common molecular finding in adult ALL
  - Seen in 50% of patients older than 60

- TKI use
  - Imatinib and dasatinib have been used concurrently with chemotherapy, though optimal timing unknown

- Transplant if possible
Transplant in Ph- ALL

- Conflicting data about allo SCT in CR1
- French LALA-87
  - 46% vs 31% 10-year survival in transplant vs. chemotherapy (p=0.04)
  - High risk patients derived most benefit from transplant
    - Ph+
    - Age > 35
    - WBC > 30,000
    - Time to CR > 4 weeks
  - Standard risk patients had comparable benefit 49% vs. 39% survival (p=0.6)
Transplant in Ph- ALL

- French LALA-94
  - High risk and patients with CNS involvement did better with transplant
  - Results confirm earlier LALA-87 trial
Transplant in Ph- all

- MRC UKALL12/ECOG 2993 Study
  - Largest prospective trial enrolling 1913 patients between 1993 and 2006
  - All patients younger than 50 (later 55) with a matched sibling donor were assigned to transplant
  - Ph+ patients were assigned to MUD transplant if no matched sib were available
- High risk
  - Age > 35 years
  - WBC > 30,000 (or >100,000 for T-cell disease)
  - Ph+ status
Transplant in Ph- ALL

- Overall survival was 53% for patients with donor vs 45% for those without (p=0.01)
- Standard risk patients derived the most benefit, 62% vs. 52% 5-year overall survival
- High risk patients did not have differing outcomes (41% vs. 35%, p=0.2)

Why?
- Maybe transplant is better
- Maybe TRM was higher in older patients
Autologous SCT

- Multiple studies incorporated auto transplant for patients without donors
- None showed a benefit of auto SCT versus chemotherapy
- No consistent role for auto SCT as a treatment for ALL
Mature B-cell ALL (Burkitt’s)

- High dose cyclophosphamide, doxorubicin, vincristine as well as intravenous methotrexate and cytarabine
- Intrathecal methotrexate and cytarabine
- No need for maintenance treatment
- High cure rates (>80% range)
- Hyper-CVAD
- Modified Magrath
  - CODOX-M (cyclophosphamide, doxorubicin, adriamycin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate)
  - IVAC (ifosfamide, cytarabine, etoposide and intrathecal methotrexate)
Adolescents and Young Adults

- 18-21 year old patients on peds regimens did better than those on adult studies (63% vs 34% 7-year EFS)

- Why?
  - Drugs? Higher doses of steroids, asparaginase, vincristine, methotrexate in peds regimens.
  - Adherence to regimen?
  - The presence of mom and dad?

- Intergroup Study CALGB 10403
  - Treats 16-39 year old patients according to peds-based protocol
Supportive Care

- Tumor lysis prevention
- Febrile neutropenia
- PCP and antiviral prophylaxis due to therapy-induced immunosuppression
- G-CSF is safe and can facilitate moving on to post-remission therapy
Relapsed Disease

- Requires multi-agent treatment to re-induce a remission
- Consolidate with transplant if possible
- Nelarabine for T-cell disease
- Very poor prognosis overall
Emerging Treatment Options

- Nelarabine
- Clofarabine
- Liposomal vincristine
- Newer TKIs
- Alemtuzumab (Campath)
- Blinatumumab (BiTE antibody)
  - CD19 and CD3 antibody that brings cytotoxic T cell into proximity with B-cell ALL cell
Questions?