A Review of Acute Lymphoblastic Leukemia/Lymphoma

Terrie Flatt, DO, MA
Director, Spanish-speaking Hematology/Oncology Program
Children's Mercy Hospital
Kansas City, MO

Disclosures

- I have nothing to disclose

Objectives

- Review the presentation of leukemia
- Review the basic evaluation of leukemia
- Review tumor lysis and its management
- Review chest masses
- Review risk stratification and outcome of ALL

Epidemiology

- Acute leukemia is the most common childhood cancer
  - Acute lymphoblastic leukemia (ALL): 75%
    - 3000 cases diagnosed annually in the US
    - Represents 23% of all childhood cancers
    - Two basic sub-types recognized by WHO
      - Pre-B cell (85% of ALL cases in the US)
      - T-Cell (10-15% of ALL cases in the US)
    - 2 peak age associated incidences: 2-5 y/o and teens
    - Racial/ethnic difference in incidence
      - Hispanic>Caucasian>Blacks
      - 35 cases annually for Caucasians and 45 cases annually for Hispanics
      - 15% increased incidence of ALL among Hispanics compared to other races
  - Acute myeloblastic leukemia (AML) : 20%
    - 500 new cases annually in the US
  - Acute undifferentiated : <0.5%
  - Acute mixed lineage : (rare)
- Chronic myeloid leukemia represents 3% of childhood leukemia
  - (Bathia et al 2000; Kadan-Lottick NS et al 2003; Swinney RM et al 2000; Margolin et al 2011)

Lymphoblastic Lymphoma

- Lymphoblastic lymphoma represents approximately 20% of all Non-Hodgkin's lymphoma
  - T-cell 15%
  - B-cell 3%

ALL: Clinical Features

- Hepatosplenomegaly 68%
- Splenomegaly 63%
- Fever 60%
- Malaise and fatigue 50%
- Lymphadenopathy 50%
- Pallor 40%
- Bleeding 48%
- Bone pain 23%
- CNS signs 5%

(Margolin et al, 2011)

ALL: Laboratory Features

- CBC
  - Platelet count
    - <20,000 28%
    - 20,000-99,000 47%
    - >99,000 25%
  - Leukocyte count
    - <10,000 53%
    - 10,000-49,000 30%
    - >50,000 17%
  - Hemoglobin
    - <7 43%
    - 7-10 45%
    - >11 12%

(Margolin et al. 2011)

High Index of Suspicion: call Hem/Onc

- Persistent fever/infections
- Skin infections that progress in spite of antibiotics
- Subcutaneous nodules (chloroma)
- Fixed, hard and matted lymph nodes
- Lymphadenopathy that does not respond to antibiotics
- Gingival hyperplasia
- Persistent wheezing, stridor, cough, change in voice (muffled, weakened)-think chest mass
- Persistent limp that inhibits activity

What to do if you suspect Leukemia/lymphoma

- The basic work-up:
  - CBC with differential and peripheral blood smear for path review
  - BMP, LFT's, uric acid, phosphorous
  - LDH
  - ESR
  - PT/PTT/Fibrinogen/D-Dimer
  - CXR

Tumor Lysis

- Definition: Break down (lysis) of fragile tumor cells that contain increased quantities of potassium, phosphorous, and protein (uric acid).

Risk for Tumor Lysis

- ***Burkitt's Lymphoma
- Leukemia, esp. lymphoblastic
- AML is less associated with this
- Lymphoma
- High WBC with high blast count
- Large spleen, liver, bulky nodes

Tumor Lysis

- Lab Findings:
  - K↑, Phos ↑, Uric Acid ↑
  - Ca↓ to normal
  - LDH ↑
  - CRT often elevated

Treatment

- Allopurinol or Rasburicase for high uric acid
  - Allopurinol: 150mg/m2/day divided TID PO or 10mg/kg/day divided TID.
  - Rasburicase: 0.2mg/kg (max dose 6 mg) IV
    - Reserved for uric acid>10, elevated CRT, high WBC
    - Do not give if G-6PD deficiency

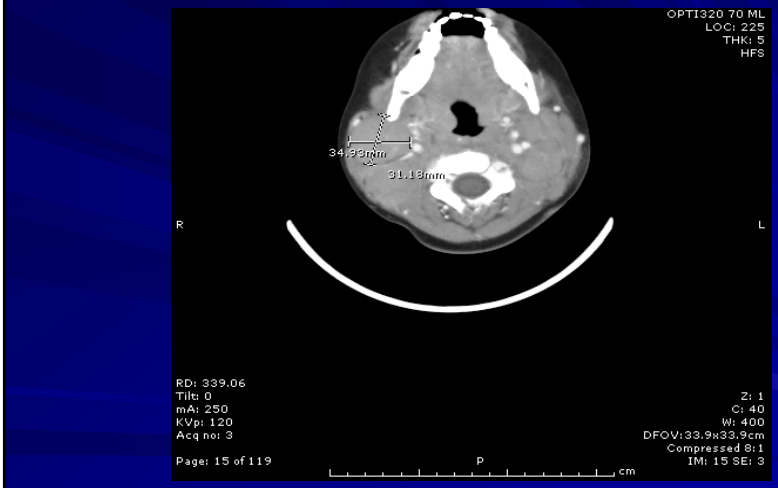
Treatment

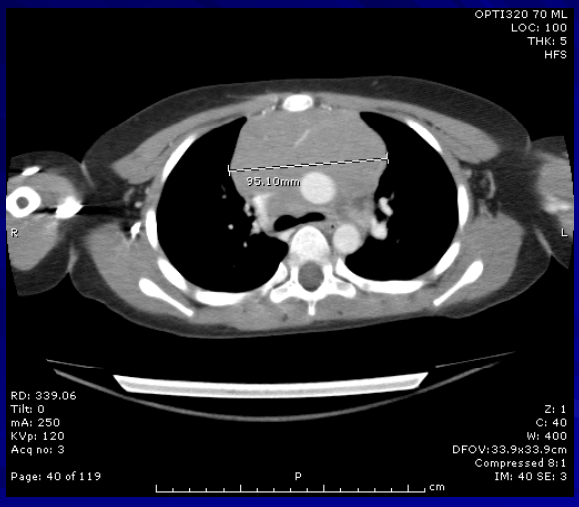
- IV Hydration (1.5 to 2 x maintenance fluids WITHOUT K+).

Some Cases to Ponder

- Case 1: 8 y/o Hispanic male presents to PCP for cervical adenopathy. CBC was obtained at initial visit which was normal. He was treated with a 2week course of broad spectrum antibiotics. Lymph nodes became larger and he developed fatigue and shortness of breath with normal activities. He returned to PCP. CBC and CT of neck/chest obtained. Immediately referred to Hem/Onc.

- CBC with second visit:
  - WBC: 9400
  - Hgb: 12
  - Plt: 319,00
  - No blasts
- CBC 2 days later
  - WBC: 249,000
  - Hgb: 11
  - Plt: 130,000
  - 127,000 absolute blasts


OPTI320 70 ML
LOC: 225
THK: 5
HFS
34.93mm
31.13mm
R
L
RD: 339.06
Tilt: 0
mA: 250
KVp: 120
Acq no: 3
Page: 15 of 119
P
cm
Z: 1
C: 40
W: 400
DFOV:33.9x33.9cm
Compressed 8:1
IM: 15 SE: 3


OPTI320 70 ML
LOC: 100
THK: 5
HFS
95.10mm
R
L
RD: 339.06
Tilt: 0
mA: 250
KVp: 120
Acq no: 3
Page: 40 of 119
P
cm
Z: 1
C: 40
W: 400
DFOV:33.9x33.9cm
Compressed 8:1
IM: 40 SE: 3

Diagnosis

- T-Cell Acute lymphoblastic leukemia

Mediastinal/Neck Mass

- Think chest/neck mass and obtain CXR
  - Persistent wheezing/SOB
  - Difficulty breathing in supine position
  - Persistent cough that does not respond to medications/antibiotics
  - “pneumonia” that never goes away with treatment
  - Stridor, especially in an older child (it ain’t natural at 10 yrs of age)
  - Superior vena cava syndrome

Mediastinal Mass

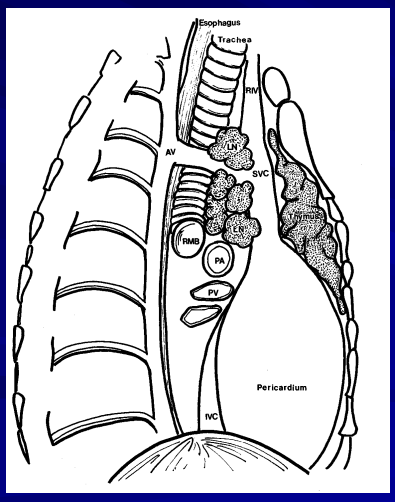
- Differential Diagnosis

Location

Location

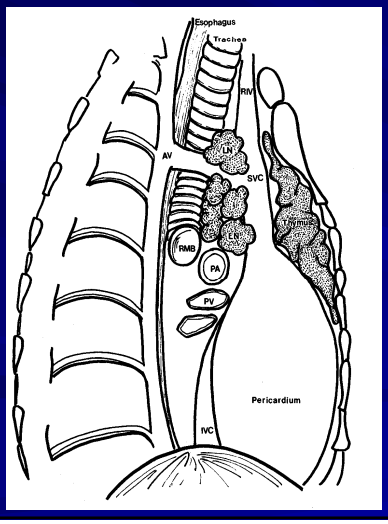
Location

Anterior Mediastinum



- DIFFERENTIAL DX?
- Lymphoma/leukemia
- Thymic tumors
- Teratoma
- Lipoma
- Thyroid tumors
- Rhabdomyosarcoma
- Germ cell tumors
- Bronchogenic cyst
- Pericardial cyst
- Metastatic disease

Posterior Mediastinum



- Tumors from nerve roots and sympathetic ganglia (neuroblastoma to ganglioneuromas)
- Ewings from spine
- Rhabdomyosarcoma arising from muscle and soft tissue
- Germ Cell Tumors

Factors associated with acute airway compromise

- 1) anterior location of the mediastinal mass
- 2) histological diagnosis of lymphoma/leukemia
- 3) symptoms and signs of superior vena cava syndrome
- 4) radiological evidence of vessel compression or displacement
- 5) pericardial effusion
- 6) pleural effusion
- 7) tracheal deviation
- 8) orthopnea

(J. C. M. Lam et al. When is a Mediastinal Mass in a Child Critical? J. of Pediatric Surg Int. 2002; 20: 2004)

Factors associated with acute airway compromise

- Tracheal compression and presence of 3 or more respiratory symptoms are the strongest predictive factors for complications with general anesthesia in a retrospective study of 60 patients with mediastinal masses (NgA, Bennett J, Bromley P, et al. Anaesthetic outcome and predictive risk factors in childrenwith mediastinal tumours. Pediatr Blood Cancer 2007;48:160–4.)

Case 2:

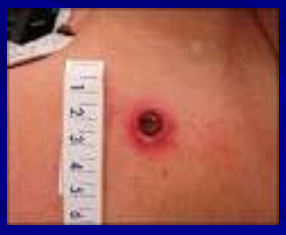
- 4 y/o male presents with lesion to right buttock. Lesion is erythematous, indurated and painful to touch. He is placed on Amoxil. He develops fever and refuses to walk due to pain. He is seen in ER for intractable pain and given Bactrim. He is unable to tolerate oral antibiotics and is seen by PCP again. Lesion is worsening and child appears ill. He has been out of the country traveling and has possible h/o spider bite.

Case 2

- CBC obtained at PCP office:
  - WBC: 1420
  - Hgb: 5.3
  - Plt: 15,000
  - No blasts

Case 2

- Admitted for infection and/or possible brown recluse spider bite.



Case 2

- Lesion cultured
  - Pseudomonal echthyma gangrenosum

Case 2

- Bone marrow aspirate performed
  - Standard risk Pre-B ALL

Case 3

- 18 y/o Caucasian female presents to PCP and ED with multiple episodes of cervical adenopathy, fatigue and sore throat. She is given several rounds of antibiotics and prednisone (60mg PO BID) on different occasions. Adenopathy improves for short periods of time and then returns after steroids are stopped. She undergoes tonsillectomy and given prednisone.

Case 3

- Several weeks after tonsillectomy she becomes extremely fatigued and pale. A CBC is performed and Hgb is 4. She is transfused. She is admitted for further evaluation. LDH, ESR and uric acid are normal. EBV titers done and are positive for acute infection and is often a culprit for myelosuppression.

Case 3

- Repeat CBC while hospitalized
  - WBC: 3900
  - Hgb: 8.5 (post-transfusion)
  - Plt: 127,000
  - No blasts

Case 3

- She was followed weekly by Hem/Onc for 3 weeks. WBC and platelet counts normalized but Hgb dropped. No blasts reported on any CBC and LDH was normal on all subsequent visits. Bone marrow biopsy and aspirate performed as anemia did not resolve.

Case 3

- Diagnosis
  - Pro-B ALL (very immature leukemia)
- Clinical course
  - Pt did not achieve remission and underwent experimental therapy and went into remission and proceeded with bone marrow transplant
  - Pro-B less favorable prognosis
  - Pre-treatment with multiple course of steroids
    - Steroid resistance in leukemia cells
    - Places PT in high risk stratification when pre-treated with steroids
    - Portends worse overall prognosis
    - On some protocols, excludes patient from participating in trial

ALL OUTCOMES

- ALL of childhood is a curable disease
  - Pre-B ALL (standard risk): 85 to 90% overall survival rate
  - T-Cell ALL: 75% overall survival rate

Prognostic Factors Affecting ALL Outcome

- Patient characteristics
- Leukemic cell characteristics
- Response to therapy

Understanding Outcome Based Upon Patient Characteristics

Favorable

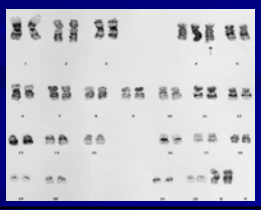
- Age: 1 to 10 years
- WBC count at diagnosis: <50,000
- No CNS involvement
- No testicular involvement
- Gender: FM better than male
- Race: Caucasian/Asian

Unfavorable

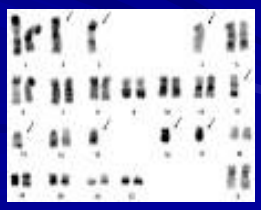
- Age: <1 or > 10 years
- WBC count at diagnosis: >50,000
- CNS 3 disease
- Testicular involvement
- Gender: Male worse than FM
- Race: Hispanic, Native American, African American
- Pre-treatment with steroids

Understanding Outcome Based Upon Characteristics of Leukemia Cells

- Favorable
- Immunophenotype
  - Pre-B ALL
- Cytogenetics
  - DNA Content
    - Hyperdiploid: 47-50 chromosomes
    - High Hyperdiploid 51-65 chromosomes



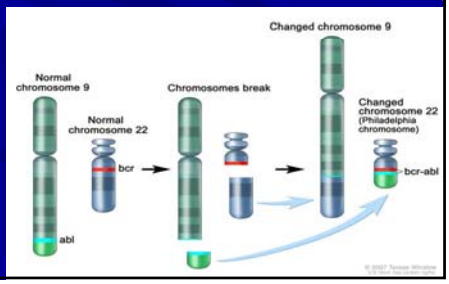
- Unfavorable
- Immunophenotype
  - T-Cell ALL
- Cytogenetics
  - DNA Content
    - Hypodiploid: <44 chromosomes



Understanding Outcome Based Upon Characteristics of Leukemia Cells

- **Favorable**
- Cytogenetics
  - Trisomy 4, 11, 17
  - Translocations
    - TEL-AML (*ETV6-RUNX1 (t(12;21)*

- **Unfavorable**
- Cytogenetics
  - Translocations
    - MLL t(4;11)
    - Chromosome 21 amplification (iamp21)
    - BCR-ABL1 t(9;22)



Understanding Outcome Based Upon Response to Therapy

- **Favorable**
  - Day PB <1% blasts
  - Day 29 bone marrow <0.01% MRD
- **Unfavorable**
  - Day PB >1% blasts
  - Day 29 bone marrow >0.01% MRD
  - Induction failure

Treatment Basics

- Length of Therapy
  - Approximately 2.5 years for females
  - Approximately 3 years for males
- Phases of Therapy
  - Induction
  - Consolidation
  - Interem Maintenance (I and II)
  - Delayed Intensification
  - Maintenance
    - Outpatient therapy
    - Return to “normal” life
    - Return to General Pediatrics for many health care related services

- Questions??
- Thank you for your time and attention

References

Bhatia S, Sather HN, Heerema NA, et al. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood 2002:100(6):1957-1964.

Kadan-Lottick NS, Ness KK, Bhatia S, et al. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. JAMA 2003:290(15):2008-2014.

Swinney RM, Beuten J, Collier AB, 3rd, et al. Polymorphisms in CYP1A1 and ethnic-specific susceptibility to acute lymphoblastic leukemia in children. Cancer Epidemiol Biomarkers Prev:2000(7):1537-1542.

Margolin , JF et al (2011). Acute lymphoblastic leukemia (518-565). Principles and Practice of Pediatric Oncology. Philadelphia: Lippincott, Williams, and Wilkins.

Gross, T, et al. Malignant Non-Hodgkin's Lymphoma in Children (663-682). Principles and Practice of Pediatric Oncology. Philadelphia: Lippincott, Williams, and Wilkins.

J. C. M. Lam et al. When is a Mediastinal Mass in a Child Critical? J. of Pediatric Surg Int. 2002; 20: 2004

NgA, Bennett J, Bromley P, et al. Anaesthetic outcome and predictive risk factors in childrenwith mediastinal tumours. Pediatr Blood Cancer 2007;48:160–4.)