Leukemia

Presentation to family medicine residents

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Goals today

• Provide general overview of leukemia for family practice residents
• Discuss clinical presentation and general treatment principles
• Provide opportunity for discussion and answering any questions

• This is an Interactive session – ask questions anytime
Definition of leukemia

• “A Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of blood cells to be produced and enter the bloodstream”.

http://www.cancer.gov/cancertopics/types/leukemia
Blood cell development
B cell neoplasms

- Multiple myeloma
- Waldenström's macroglobulinemia
- Hodgkin's lymphoma
- Follicular center cell
- Mantle cell lymphoma
- Pre-B cell leukemia
- Acute lymphoblastic leukemia
- Chronic lymphocytic leukemia (CLL)

<table>
<thead>
<tr>
<th>Name of tumor</th>
<th>Normal cell equivalent</th>
<th>Location</th>
<th>Status of Ig</th>
<th>V genes</th>
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<tbody>
<tr>
<td>Multiple myeloma</td>
<td>Plasma cell</td>
<td>Various isotypes</td>
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<td>Waldenström's</td>
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<td>Acute lymphoblastic leukemia</td>
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<td>Chronic lymphocytic leukemia (CLL)</td>
<td>CD5 B1 cell</td>
<td>B cell</td>
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</tbody>
</table>

- Bone marrow
- Peripheral
- Usually unmutated
Incidence

- Estimated new cases and deaths from leukemia in the United States in 2010:
  - New cases: 43,050
  - Deaths: 21,840

http://www.cancer.gov/cancertopics/types/leukemia
Leukocytosis: Causes

- Infection
- Inflammation: tissue necrosis, infarction, burns, arthritis
- Stress: overexertion, seizures, anxiety, anesthesia
- Drugs: corticosteroids, lithium, beta agonists
- splenectomy
- Hemolytic anemia
- Leukemoid reaction to solid malignancy
- Bone marrow problems
  - Acute leukemia
  - Chronic leukemia
  - Myeloproliferative disorders
Role of a family physician

- Identify the cause of leukocytosis based on
  - Symptoms
  - Initial history and physical examination
  - A complete blood count
- Inflammation or infection response: most of the cells are polymorphonuclear leukocytes.
- Suspect a primary bone marrow disorder
  - in patients who present with extremely elevated white blood cell counts
  - concurrent abnormalities in red blood cell or platelet counts.
  - Weight loss, lethargy, bleeding or bruising
  - liver, spleen or lymph node enlargement,
  - immunosuppression and repeated infections
- Refer patient to a specialist in timely manner
Risk factors / causes of leukemia

- Risk is increased in
  - Fanconi’s anemia
  - Ataxia telangetasia
  - Bloom’s syndrome
  - Down’s syndrome
  - Infantile x linked agammaglobulinemia
- Oncogenic virus
  - HTLV-1: causative agent for Adult T cell leukemia
- Radiation exposure - Increased risk of AML, CML and ALL
- Chemicals: Benzene, Carbon tetrachloride, Kerosene
- Drugs: Melphalan, CCNU, Alkylators, Etoposide
- Myelo-dysplastic syndrome
Types of leukemia

Leukemia

Acute
- acute nonlymphocytic leukemia
- acute lymphocytic leukemia

Chronic
- chronic lymphocytic leukemia
- chronic myeloid leukemia
- Others
Leukemia: General symptoms

• An Acute leukemia patient is more likely to be ill at presentation
• Acute leukemia can be very rapidly fatal
• White blood cell counts above 100,000 per mm$^3$ represent a medical emergency: Risk of hemorrhage and CNS complications.
• A chronic leukemia patient is likely to be diagnosed incidentally because of abnormal blood cell counts
## Leukemia: Common presentations

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptom</th>
<th>Signs</th>
<th>Lab findings</th>
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<td>Anemia</td>
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Acute leukemia
Acute leukemia

• Clonal uncontrolled proliferation of marrow cells
• Blast cells are seen in marrow and blood
• Loss of normal marrow function
• Characterized by acquired abnormalities in chromosomes – number or stricture
• Diagnostic methods
  • Review of peripheral smear
  • Bone marrow histology
  • Immunophenotyping
  • Chromosome analysis
  • Molecular marker studies: FISH, PCR etc.
AML
Acute myeloid leukemia (AML)

- Most common adult leukemia
- Incidence increase with age – 12 fold increase around age 70
- Idiopathic AML has better prognosis than secondary (treatment related or MDS related AML)
- Auer rods, are a marker of acute nonlymphocytic leukemia and seen sometimes (not always).
- FAB classification: 7 subtypes M1-M7
Auer rods

http://commons.wikimedia.org/wiki/File:Auer_rods.PNG
AML cells

http://pathy.med.nagoya-u.ac.jp/atlas/img/t6/img022.jpg
Acute myeloid leukemia (AML)

- Risk factors
  - Prior chemotherapy
  - Prior myelo dysplasia
  - Radiation exposure
  - Down’s syndrome
- Chemicals
  - Benzene
  - Herbicides
  - Pesticides
  - smoking
Acute myeloid leukemia (AML)

- Prognostic factors
- Cytogenetics – most powerful predictors
- Favorable
  - M3 -t(15, 17)
  - M4-inv (16)
  - M2- t(8,21)
  - Young age
  - Low WBC at presentation
- Intermediate
- Unfavorable
  - Loss or deletion of chromosome 5 or 7
  - Trisomy 8
  - Old age
  - High WBC at presentation
AML: Chemotherapy

• Induction therapy:
  • To achieve marrow aplasia and clear leukemic cells
  • Ara-c with an Anthracycline is used as first line
  • Patients requires intensive supportive care
  • GM-CSF may be used to help blood cell recovery
  • Patient with residual blasts are re-treated with repeated chemotherapy
  • Overall 60-80% may achieve remission
  • Failure to achieve normal cytogenetics predicts poor outcome
AML: Chemotherapy

- Consolidation (post remission therapy)
  - Given to patients with no evidence of leukemia on marrow biopsy after induction
  - However, occult leukemia persists
  - Consolidation is given with high dose Ara-c to prevent relapse
  - Some patients may be candidates for bone marrow transplant or stem cell transplant after consolidation Ara-C
  - Patients less than 50 with compatible sibling match usually get BMT in first remission
  - Allogeneic transplant: induces Graft versus host disease
Newer therapies in AML

- Gemtuzumab
- An anti CD 33 antibody – immunotoxin
- Used in relapsed elderly patients
- Fewer infections than conventional chemotherapy
- Unique hepatic toxicity – hepatic sinusoidal injury syndrome
- Many other targeted therapies are being investigated
AML-M3: APL

- Acute promyelocytic leukemia (APL)
- Curable in 80% cases
- Less than 10% of AML cases
- Seen in younger patients
- Hemorrhagic syndrome – a common complication
- Characteristic translocation t (15,17)
- Exquisitely sensitive to Anthracycline: high risk of death during induction from bleeding
- All trans retinoic acid (ATRA) and Arsenic: High cure and salvage rates
- ATRA corrects coagulation problems inmost
- ATRA complication: Hyper-leukocytosis – needs steroids
Granules in M3 cells

Acute lymphocytic leukemia (ALL)

- FAB classification: 3 subtypes L1-L3
- Most ALLs express CALLA antigen (early B cell antigen)
- 20% express T cell antigens
- 15-20% adult ALL has Philadelphia chromosome (Ph -190kDa))
- Acute lymphocytic leukemia most commonly occurs in children less than 18 years of age.
- Neonatal ALL: t(4,11)
- L3 ALL: t(4,11)
- Gain of chromosomes (hyperploidy): favorable prognosis
- T cell ALL : mediastinal mass is more common
ALL cells

http://pathy.med.nagoya-u.ac.jp/atlas/img/t8/img76.jpg
ALL-L3

http://pathy.med.nagoya-u.ac.jp/atlas/img/t8/img81.jpg
ALL Prognostic factors

- Cytogenetics – most powerful predictors
- Favorable
  - Hyperploidy
  - Young age
  - Low WBC at presentation
  - Absence of myeloid antigens
  - Early complete remission
- Unfavorable
  - Myeloid antigen expression
  - Ph chromosome, t(4,11), t(8,14), t(1,19)
  - Old age
  - High WBC at presentation
ALL chemotherapy

- Up to 90% complete remission rate
- Children respond better than adults
- Therapy:
  - Induction: Intensive combination regimen such as VAD
  - Post-remission therapy: prolonged regimen
  - CNS prophylaxis: necessary
  - Intensive supportive care is necessary
  - Bone marrow transplant
    - For ALL resistant to standard therapy
Supportive care
Supportive care in acute leukemia

• Needed for all patients
• Transfusion support
  • Red blood cell transfusions
  • Platelet transfusions
    • ASCO suggests threshold of approximately 10,000 without other risk factors
    • Lumbar puncture requires at least more than 20,000
• Treatment of infections: Bacterial, fungal, viral, unusual
  • Antibiotics and anti-virals
  • Prophylaxis
• Hydration - Electrolyte replacement
• Psychological support
Transfusion support in acute leukemia

• Transfusions are indicated to treat bleeding patients
• Prophylactic platelet transfusions
  • A platelets count below 10,000
  • A higher threshold below 20,000 for patients with fever, disseminated intravascular coagulation, and mucositis secondary to chemotherapy
• Packed RBC transfusions
  • Hemoglobin generally below 8
  • Symptomatic anemia
  • Bleeding
• Granulocyte transfusions
  • No proven benefit as prophylaxis
  • Rarely used in neutropenic patients serious sepsis
Chronic leukemia
CLL
Chronic lymphocytic leukemia (CLL)

- Abnormal proliferation of mature lymphocytes with immunophenotype of CD 5+, CD 20+ and CD 23+ CD 10 negative B lymphocytes
- Present in blood, bone marrow and lymphatic tissue
- Small lymphocytic lymphoma (SLL) is lymphomatous counterpart of CLL
- Incidence increases with age
- Often asymptomatic, incidental detection on CBC
- Primarily in age over 40 years
- Lymphocytosis: over 5000 lymphocytes on multiple occasions in CBC differential
- Many have long periods of stability or slow progression
CLL cells

http://commons.wikimedia.org/wiki/File:Chronic_lymphocytic_leukemia.jpg
CLL diagnosis

- Diagnosis: By flow cytometry – can be done in peripheral blood or bone marrow
- CD 38 is a prognostic factor
- Cytogenetics: Trisomy 12 is most common
- Immunoglobulin heavy chain variable region mutations: Indolent course – median survival of about 25 years
- Immunoglobulin heavy chain variable region genes unmutated: (Surrogate marker is ZAP 70): Worse prognosis – med survival of about 8 years
- Short doubling time, advanced age, high B2 microglobulin are also poor prognosticators
CLL stage

- Rai and Binet systems
- Rai staging
  - Stage 0: Lymphocytosis
  - Stage 1: Lymphocytosis + Adenopathy
  - Stage 3, 4: Lymphocytosis + Anemia and/or thrombocytopenia
- Correlates with median survival
  - Stage 0: over 10 years
  - Stage 1: 7 years
  - Stage 3, 4: 1.5 years
- Overall median survival is 10-14 years
CLL features

- B symptoms: Fever, drenching night sweats, weight loss
- Lymphadenopathy
- Splenomegaly
- Hemolytic anemia: positive direct coomb’s test, low haptoglobin, indirect billirubinemia
- Thrombocytopenia – immune or marrow infiltration
- Infections: Depressed immunoglobulins
- Bleeding
- Transformation to more aggressive lymphoma (Richter’s syndrome) or aggressive leukemia
CLL treatments

- Watchful waiting
- Anti CD 20 antibody Rituximab
- Chemotherapy: Oral or IV with or without steroids
- Combination chemotherapy
- Experimental treatments such as new targeted drugs, bone marrow transplant etc.
- Treatment is reserved for certain clinical situations
  - Disease related symptoms: nodes, liver, spleen, B symptoms
  - Marrow failure
  - Auto immune anemia
  - Immune thrombocytopenia
  - Recurrent infections
CLL immune defects

• Impaired immunity and increase in infection risk
  • IVIG may decrease bacterial infections but does not affect survival
  • Reserved for selected patients

• Immune cytopenias
  • Autoimmune hemolytic anemia
    • Steroids or chemotherapy
  • Immune Thrombocytopenia
    • Steroids or chemotherapy
Hairy cell leukemia

- Generally in older male patients
- Characterized by splenomegaly, pancytopenia and marrow infiltration with atypical lymphoid cells with cytoplasmic projections (hairy cells – B cells CD 19, 20 positive))
- Stain positive with tartrate resistant acid phosphatase (TRAP)
- Bone marrow is fibrotic
- Prolonged remission can occur with treatment with purine analogues such as Cladarabine (2-CDA) or Pentostatin (DCF) or interferon
- Splenectomy is rarely done these days
- Anti CD 22 antibody is promising treatment
Hairy cell leukemia

Chronic myeloid leukemia (CML)

- Prototype myelo-proliferative disorder
- Hallmark of CML: A balanced translocation between chromosomes 9 and 22 (Philadelphia chromosome)
- Ph creates a unique gene (BCR-ABL) which encodes a 210 kDa protein (p210) functioning as a tyrosine kinase
- Diagnostic of CML
- Causative genetic event in CM
- All hematopoietic cells contain BCR-ABL (Clonal at stem cell)
- Conventional treatments: Hydroxyurea, Interferon, BMT
CML cells
CML

- Proliferative phase (driven by BCR-ABL)
  - Leukocytosis on routine CBC
  - Fatigue, weight loss, splenomegaly, thrombocytosis
  - T (9,22) can be detected by karyotyping, FISH or PCR in blood or bone marrow

- Accelerated phase

- Blast crisis:
  - Progression to acute leukemia type picture
  - additional genetic abnormalities are acquired
  - Rapidly fatal if untreated
Philadelphia chromosome. A piece of chromosome 9 and a piece of chromosome 22 break off and trade places. The bcr-abl gene is formed on chromosome 22 where the piece of chromosome 9 attaches. The changed chromosome 22 is called the Philadelphia chromosome.

http://www.cancer.gov/cancertopics/pdq/treatment/adultALL/patient
CML – Imatinib treatment

- Imatinib is targeted drug – inhibits BCR-ABL tyrosine kinase and suppresses CML clone
- 95% patient achieved complete hematological remission
- Better tolerated than interferon type treatments
- 85% complete cytogenetic remission
- About 4% annual relapse rate
- Side effects: Nausea, muscle cramps, rare hepatic-toxicity, fluid retention
- Optimal duration is unclear
- Low risk of relapse remains
- Hydroxyurea can be used to control blood counts
- Newer better drugs are in development
CML

- Allogeneic Bone marrow transplant can result in long term survival
- Best results in early chronic phase
- Less used now a days because of success of Imatinib
Chronic Myelo-monocytic leukemia (CMMoL)

- CMMoL is a myelo-dysplastic syndrome
- Proliferation of mature myeloid and monocytic cells
- Not to be confused with CML
- Splenomegaly
- Treatment is control of blood counts with Hydroxyurea
Long term survivors

- Long term ALL survivors
- Higher than normal risk of second malignancies
- Monitor for long term treatment effects
THANK YOU

THE END