Acute and Chronic Leukemias

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Objectives

• Understand what leukemias are and how they occur
• Be able to differentiate between acute and chronic leukemias when referring to presentation, prognosis, course, and treatment.
• Achieve a general understanding of how leukemias are classified and the implications of genetic abnormalities found in these diseases
Objectives

• Know the most common agents used for treating different leukemias
  – MOA, unique side effects, special management considerations, etc

• Be familiar with adjunct agents used in the treatment of leukemias
  – Antiemetics, growth factors, chemoprotectants, etc

• Know medical problems and emergencies that occur with leukemias and their management
Hematopoiesis

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Definition

• Leukemias
  – Heterogeneous group of diseases characterized by the abnormal proliferation of white blood cells
  – Named or typed based on hematopoietic origin
  – Clonal cell population
  – May have distinct genetic abnormalities
  – Differing levels of clonal maturity
Leukemogenesis

• Requires multiple steps to occur and may be due to defects in cell growth, differentiation, and/or death
• Initial insult may be viral, chemical, radiation, genetically destined, or unknown
• In general the balance is lost between proliferation, differentiation, and maturation
Leukemogenesis

- Malignant clone outgrows normal cells
- Clone may:
  - Lose response to normal cell regulation
  - Lose ability to differentiate/mature
  - Grow at the expense of normal cells
  - Suppress or impair normal cell growth
Cytogenetics

• Majority of leukemias have acquired cytogenetic (chromosomal) abnormalities which may disappear with disease remission
• Cytogenetics frequently have therapeutic and prognostic implications
• Types of abnormalities
  – Numerical – gain or loss of one or more chromosomes
  – Structural – exchanges of information between (translocations) or within chromosomes (inversions)
Chromosomal Nomenclature

• “p” - refers to short arm of the chromosome and “q” refers to the long arm

• A “+” or “-” written before the chromosome number means you have an extra (+) or are missing (-) one e.g. Trisomy 12 = +12

• A + or - written after the p or q indicates a shortening (-) or lengthening (+) of the short or long arm. e.g. 13q- refers to a diminished long arm of chromosome 13

• A number after the p or q refers the band number on the chromosome e.g 13q23 refers to an abnormality on the long arm of the 13th chromosome at the 23rd band.
Molecular Mechanisms of Leukemia

• Multiple possible mechanisms
  – Alteration of normal gene (proto-oncogene) creates a cancer promoting novel gene (oncogene) – RAS, BCL
  – Loss/inactivation of cancer suppressing gene (anti-oncogene) - RB1, P-53
  – Chromosomal change creates a novel protein/enzyme – BCR-ABL

• Molecular categorization identifies targets for rationally designed (“targeted”) therapy
Incidence in the US

• Acute Leukemias are 3% of all cancers (30-35% in children)
• Acute Myeloid Leukemia (AML, ANLL)
  ~13,400 cases/yr
• Acute Lymphocytic Leukemia (ALL)
  ~5200 cases/yr
• Chronic Myelogenous Leukemia (CML)
  ~4600 cases/yr
• Chronic Lymphocytic Leukemia (CLL)
  ~15,300 cases/yr

Pickle LW et al CA, Cancer Jnl Clin 2007;57:30-42
Acute Leukemia Survival

- In 1951 average of 20 weeks
- Untreated acute leukemias have life expectancy of weeks and chronic leukemias generally 1 to multiple years
- Disease Free Survival (DFS)
  - Adults 75%
  - Children 33%
General Demographics

• Acute leukemias are more common in men (1.5:1)
• In US
  – Acute leukemias more common in whites than blacks
  – AML - higher incidence in higher socioeconomic groups
• Median age of diagnosis (years)
  – AML 63
  – ALL 10
Acute Lymphocytic Leukemia (ALL)

• 10-20% of adult and 80% of childhood acute leukemias
• Clonal proliferation of lymphoid progenitors
• 1.3/100,000 population/yr
ALL Etiology

• Ionizing radiation - not electromagnetic fields
• Drugs – Chloramphenicol
• Viral – HTLV-1
• Heredity – 2X incidence in siblings, 25% of identical twins
• Genetic – Down syndrome, Bloom syndrome, Fanconi anemia, Kleinfelter’s syndrome
• Most of unknown etiology
Clinical Features

- Malaise, fever, lethargy, weight loss, night sweats, bone pain
- Infections, hemorrhage, lymphadenopathy, splenomegaly, hepatomegaly (50%)
- CNS involvement, Thymic mass
- ANC < 1500, thrombocytopenia, anemia, WBC (low-33%, high-67%)
FAB Classification

- **L1 (homogenous cell population)**
  - Early Pre B, Pre B, B cell, T cell
  - 85% children, 30% adults
- **L2 (heterogeneous cell population)**
  - Early Pre B, Pre B, B cell, T cell
  - Most common adult type (60%, Children 14%)
- **L3 (Burkitt Like)**
  - B cell, 10% of adults and 1% of children

FAB – French-American-British
Prognosis

• **Good**
  - T-cell, Pre-B cell
  - Normal cytogenetics, Translocations of chromosomes 12 and 21\{t(12:21)\} or TEL-AML-1, hyperploidy(50-60 chromosomes), t(10:14), del 12p

• **Poor**
  - White blood cell count > 30K
  - Age > 60 (< 1 or > 10 in pediatrics)
  - L3
  - Philadelphia Chromosome + t(9:22), t(1:19), t(4:11), t(8:14), trisomy 8, hypodiploid
  - Mature B cell type
  - > 4-5 weeks to CR
Components of Therapy

- Empiric multi-agent chemotherapy
- Pre-symptomatic CNS Therapy
- Post-induction intensification
- Risk adapted therapy choices
  - High risk prognosis receives more aggressive therapy
Treatment-1

- **Induction Therapy**
- Vincristine and prednisone – 50% response rate lasting 3-12 months
- Adding Daunorubicin and L-Asparaginase increased response to 83%
- All patients now receive either 3 or 4 agents
- Add imatinib if t(9:22) i.e. Ph+

- **Complete Remission (CR)** - <5% blasts and no symptoms
- **Partial Remission (PR)** – 5-25% blasts
Central Nervous System Treatment

- Serves as a sanctuary site for leukemia
- Without CNS treatment >50% will relapse within 2 years
- Treatment can be intrathecal chemotherapy (methotrexate, cytarabine) or cranial radiation (5-10%)
- High dose systemic methotrexate & cytarabine may partially treat CNS
Treatment-2

- **Consolidation therapy** – Lasts 7-12 months
- Drugs used include combinations of daunorubicin, vincristine, prednisone, asparaginase, methotrexate, cytarabine, doxorubicin, mercaptopurine, and thioguanine
- Many different combinations are used per specified regimens with none used universally
Treatment-3

- **Maintenance Therapy**
  - Duration of 1.5 to 2 years
- Commonly used agents include: mercaptopurine, methotrexate, vincristine, and prednisone.
- Doses are lower than consolidation therapy
- Benefits are better validated in pediatrics than in adults
Salvage Therapy

• Allogeneic Hematopoietic Stem Cell Transplant (HSCT, aka BMT)
  – Better than chemotherapy for relapsed disease
  – Used early post induction for poor prognosis disease
  – Only option for progressive disease

• Autologous HSCT
  – Equal efficacy to maintenance therapy but of shorter duration
  – Used only in the setting of a clinical trial currently
CNS Prophylaxis

- Cranial irradiation – Long term effects
  - Mental retardation, decreased intellect and academic achievement, leukoencephalopathy
  - Minimize or delay when possible, especially in younger patients
- Intrathecal chemotherapy- methotrexate & cytarabine +/- high dose (HD) systemic chemo
- Start during induction and continue through maintenance depending on patient risk of relapse
- Decreases relapse from 50-75% to ~5%
Acute Myelogenous Leukemia (AML, ANLL)

- 80-90% of adult acute leukemias
- Median age 63 years old
- Slight male predominance
- ~3.5 cases per 100,000 individuals at 50 y/o but incidence increases with age
  - By age 70 it is ~15/100,000 individuals
AML Etiology

• Majority unknown
• Environmental contamination
  – Radiation
  – Benzene
  – Radon
  – Cigarette smoking
• Chemotherapy – alkylating agents, topoisomerase II inhibitors
• Viral?
• Heredity – Fanconi anemia, Down’s syndrome, Bloom syndrome, and others
Clinical Features

- Symptoms – Fatigue, bruising, bleeding (33%),
- Infections 25%
- Splenomegaly, hepatomegaly, (< 25%) lymphadenopathy (rare), CNS symptoms rare
- Skin (chloroma), gingival infiltration
- WBC – 33% elevated (10% very high)
- ANC always low, < 1500 at least 50%, platelets < 50K in > 50%
- Blasts seen on CBC differential, > 30%
  - Chromosomal rearrangements common
FAB Classification

- M0 – Acute Undifferentiated Leukemia
- M1 – Acute Myeloblastic Leukemia w/o maturation
- M2 - Acute Myeloblastic Leukemia w/ maturation
- M3 - Acute Promyelocytic Leukemia (APL)
- M4 - Acute Myelomonocytic Leukemia
- M5 - Acute Monocytic Leukemia
- M6 – Erythroleukemia
- M7 – Megakaryoblastic Leukemia
Prognosis

• If normal cytogenetics
  – M1-M4 better
  – M0, M5-M7 worse

• Number and type of abnormalities
  – Favorable t(8:21), t(15:17), t(9:11), inv 16, NPM1, CEBPA
  – Unfavorable t(1:22), trisomy 8, 21, monosomy 7, 21, inv 3, del 5, Flt-3 +,

• Negative Factors
  – CNS symptoms at diagnosis
  – Preceding myelodysplasia
  – Age > 60 or < 2
  – Secondary leukemia
  – High MDR1 expression
  – Abnormal Cytogenetics
  – M-6 or 7
  – LDH > 3 ULN
Treatment-1

• **Induction**

• Anthracycline x 3 days (Daunorubicin, idarubicin, or mitoxantrone) + Cytarabine X 7 days (ie 3 + 7)

• May include etoposide

• Acute Promyelocytic Leukemia receives PO Tretinoin with anthracycline ± cytarabine
Treatment - 2

- **Consolidation**
- High dose cytarabine (2-3 gm/m²) preferred
  - 40-60% CR at 3 years
- Anthracycline + tretinoin ± cytarabine for APL
  - ~40% CR at 3 years
  - Arsenic trioxide an option
- Duration 1-4 cycles
Allogeneic HSCT

- An allogeneic transplant in first CR decreases relapse from 60% to 15-20%
- Transplant early (ie in CR-1) in patients < 50 y/o with poor prognosis cytogenetics in place of consolidation
- Transplant related mortality ~20% due to treatment toxicity and immune suppression
- Graft vs leukemia effects cure
Allo HSCT - 2

- Busulfan/Cyclophosphamide and Total Body Irradiation/Cyclophosphamide are equivalent regimens, < 20% relapse rates
- Best results with HLA identical sibling donor
  - 25-30% of people have sibling match
  - Ablative HSCT rarely done over age 60
  - Increased use of Reduced Intensity (RIT) HSCT in > 60 y/o
Autologous HSCT

• Decreased mortality
  – No GVHD, immune suppression
• Increased relapse rate
  – No GVL effect
• Bone marrow purging & post transplant immune modulation are attempts to decrease relapse
Refractory/Relapsed Leukemia

• A second CR is possible in about 50% of patients but will be of shorter duration
• Allo HSCT is needed for a cure
• Other options include chemotherapy, gemtuzumab, experimental agents, or clinical trials, but cure unlikely
• APL – arsenic trioxide may be used as salvage therapy
Acute Leukemias: Goals of Therapy

- Leukemia clone eradication (CR)
- Restore normal hematopoiesis
- Infection prevention/treatment
- Transfusion support (RBC & platelets)
- Manage paraneoplastic syndromes (TLS, DIC, etc)
Chronic Lymphocytic Leukemia (CLL)

• Most common adult leukemia
• Incidence increases with age, majority > 60
• Men:Women 2:1
• More common if European descent than Asian or African
• Generally indolent course with median survival 4-6 years but can vary from 1-20 years depending on subtype
CLL

• Not associated with exposure to radiation, alkylating agents, viruses, or chemicals
• It is more common in some occupations and some families have a 2-3 fold higher incidence than general population
• Monoclonal disorder with mature cells in G0 arrest. Apoptosis is blocked and cells accumulate in lymph nodes and spleen
Clinical Features

- Malaise, fatigue, decreased exercise tolerance, 25% asymptomatic
- Lymphadenopathy, hepatomegaly, splenomegaly
- Advanced disease – anemia, thrombocytopenia, lymphadenopathy, infections
- Hypogammaglobulinemia common
Classification

• Rai & Binet staging systems – based on degree of organ involvement and bone marrow effects
• Occurs in B (95%) and T cell variants
• Patterns of bone marrow involvement
  – Nodular 10% - favorable
  – Interstitial 33%
  – Mixed nodular/interstitial 30% - favorable
  – Diffuse 25% - worse outlook
### Staging: Rai and Binet staging systems for CLL

#### Clinical staging systems for CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Value</th>
<th>Rai</th>
<th>Binet</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lymphocytosis (&gt;15,000/mm³)</td>
<td>0</td>
<td>—</td>
<td>150 months (12.5 years)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytosis plus nodal involvement</td>
<td>I</td>
<td>A &lt;3 node groups</td>
<td>101-108 months (8.5-9 years)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytosis plus organomegaly</td>
<td>II</td>
<td>B &gt;3 node groups</td>
<td>60-71 months (5-6 years)</td>
</tr>
<tr>
<td></td>
<td>Anemia (RBCs)</td>
<td>III</td>
<td>Hgb &lt;11 g/dL</td>
<td>19-24 months (1.5-2 years)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytosis plus thrombocytopenia (platelets)</td>
<td>IV</td>
<td>C PLT &lt;100,000/mm³</td>
<td></td>
</tr>
</tbody>
</table>

CLL Prognosis

- Most common chromosomal abnormalities occur in chromosomes 12 & 14

- Negative factors
  - Lymphocyte doubling time < 12 months
  - Pattern of bone marrow involvement
  - T-Cell
  - Number and type of chromosomal abnormalities
  - Stage at diagnosis (Elevated serum B-2 microglobulin - increases with disease bulk)
  - Unmutated immunoglobulin heavy chain gene
  - Expression of zeta-associated protein (ZAP 70)
  - Transformed CLL to lymphoma or pro-lymphocytic leukemia
Treatment - 1

• Watch and wait vs treat
• Indications for treatment
  – Constitutional symptoms
  – Symptomatic lymphadenopathy or hepatosplenomegaly
  – Peripheral lymphocyte doubling time < 6 mo
  – Progressive marrow failure
    • Anemia (HgB < 10)
    • Thrombocytopenia (< 100K)
  – WBC > 100K (i.e. lymphocytosis)
Treatment - 2

- Chlorambucil +/- prednisone
- Combination chemotherapy (CHOP, CVP)
- Purine analogues
  - Fludarabine – current drug of choice
  - Cladribine
  - Pentostatin – adenosine deaminase inhibitor
- All cause myelosuppression, lymphopenia, and increased risk of opportunistic infections
Treatment - 3

• Monoclonal antibodies (MAB)
  – Rituximab – Anti CD-20 MAB used in combination therapy which decreases bcl-2 expression and increases response rate and duration
  – Alemtuzumab – Anti CD-52 MAB approved as salvage therapy

• Toxicity – Infusion related side effects (fever, hypotension, allergic reactions)
Newer Combinations

- Combining alkylator with purine analogue decreases cells ability to repair alkylator damage
- MABs can further sensitize cells to chemotherapy effects

- FCR (fludarabine, cyclophosphamide, rituximab)
- PCR (pentostatin, cyclophosphamide, rituximab)
Treatment - 4

• Autologous HSCT ineffective due to rapid and frequent relapse
• Allogeneic HSCT has been used in the rare young case but too toxic in most of the elderly (> 60)
• Non-Myeloablative allogeneic HSCT are being investigated currently
  – Graft vs. leukemia results are quite delayed (8-12 mo) but curative
• New Therapies
  – Lenalidomide, arsenic trioxide
Chronic Myelogenous Leukemia (CML)

- Reciprocal translocation of chromosomes 9 and 22 creates a novel fusion protein known as BCR-ABL (Philadelphia Chromosome, PH+)
- This protein is an active tyrosine kinase which drives cellular proliferation continuously
CML

• Three disease phases
  – Chronic – indolent phase
  – Accelerated – disease accelerates toward an acute leukemic state
  – Blastic – Acute leukemia which can be either myeloid or lymphoid
CML Etiology

- 15-20% of adult leukemias and is very rare in children
- Median age of 50 with slight male predominance
- Radiation exposure
- Benzene exposure
- Others unknown without other hereditary, infectious, or chemical causes
Clinical Presentation

- Fatigue, malaise, weight loss, night sweats
- Left upper quadrant fullness/splenomegaly
- Blast phase presents with all of these at greater intensity similar to an acute leukemia
- Historically median time in chronic phase is 3 years with blast phase occurring at ~ 4 years
  - New treatments are changing the expected course of the disease
CML Prognosis

- Sokal or Hasford score
- Ph+ variations (p190, p210, p230)
- Additional cytogenetic abnormalities (+8, +19, -17q)
- Imatinib resistant clonal mutation
  - Acquisition of mutation in BCR-ABL
  - Increased number of copies of BCR-ABL
Treatment - 1

- **Chronic Phase**
- Imatinib mesylate – specific competitive inhibitor of the inactive conformation of BCR-ABL tyrosine kinase (TKI)
  - 400 mg PO daily
- Dasatinib – Inhibits BCR-ABL (325 X > imatinib) and SRC kinases
  - 100 mg PO daily or 70 mg BID
- Nilotinib - Inhibits BCR-ABL (30 X > imatinib)
  - 400 mg PO BID
Treatment -2

• Interferon alpha – 5 million units/m^2/day goal dose. Now 3^{rd} or 4^{th} line.
• Hydroxyurea – ribonucleotide reductase inhibitor used to reduce white counts
Treatment Response

- **Complete Hematologic Response (CHR)**—normalization of white cell, red cell, and platelet counts
- **Complete Cytogenetic Response (CCyR)**—Disappearance of the Ph+ from white blood cells
- **Complete Molecular Response (CMR)**—Disappearance of Ph+ at the molecular level
- If no cytogenetic response by 6 months of imatinib it is considered refractory disease
Newly Diagnosed Ph+ CML

Imatinib Based therapy

Yes 3 month CHR

Yes Continue

No Allogeneic bone marrow transplant

Yes 6 month > Partial CCyR

Yes Continue

No Change to dasatinib

Yes 9 month CCyR

Yes Continue

No Increase to 800 mg/day, consider dasatinib

Yes 12 month CCyR

Yes Continue

No Consider high dose therapy or allogeneic HSCT, if no donor or unsuitable for HSCT then dasatinib/nilotinib
Treatment - 3

- Median survival of 5-6 years on interferon. Response with imatinib still not fully characterized but it is now the first line agent of choice at 400-800 mg/day.
- Most responders still have residual disease at a molecular level
- 2-3%/yr become imatinib-resistant or accelerate to more aggressive disease
  - The risk of progression decreases with each additional year of stable disease on imatinib
- Dasatinib, a dual action TKI, or nilotinib a more potent BCR-ABL inhibitor, is used for imatinib resistant or intolerant CML patients
  - Second generation TKIs inhibit BCR-ABL in both active and inactive conformations
Treatment - 4

- Allogeneic HSCT currently the only cure for CML
  - Ablative or nonablative used
  - 50-70% transplanted in first CR will have long term survival
- Autologous HSCT can be used but relapse more frequent
Treatment - 5

• Accelerated Phase Treatment
  – Increase imatinib dose
  – Change to or use dasatinib, nilotinib
• Add cytotoxic agents
• Add interferon alfa
• Add novel therapy (arsenic trioxide, phase I agents, new TKIs or aurora kinase inhibitors)
Treatment - 6

- Blast Phase treated with dasatinib or as an acute leukemia with the appropriate therapy for a myeloid or lymphoid lineage. Cure would then require a transplant
- Hydroxyurea and plasmaphoresis may be needed to reduce white blood cell counts initially
- 20-30% will enter a 2nd chronic phase
TKI Side Effects

• Imatinib
  – Myelosuppression
  – Edema
  – Rash
  – LFT abnormalities
  – GI upset

• Dasatinib
  – Pleural effusions
  – More myelosuppressive
  – Additional side effects similar to imatinib

• Nilotinib
  – GI upset
  – QTc prolongation
  – Additional side effects similar to imatinib