Acute Leukemias in Adults – Putting the Pedal to the Metal

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Presented Saturday Sep 28th, 2019
## Disclosures

<table>
<thead>
<tr>
<th>Relationships</th>
<th>Companies or interests</th>
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<tbody>
<tr>
<td>Employment/leadership</td>
<td>None</td>
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<tr>
<td>Intellectual rights/inventor or patent holder</td>
<td>None</td>
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<tr>
<td>Consultant/Advisory role</td>
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<tr>
<td>Speaking Honouraria</td>
<td>Pfizer, Janssen, Teva, Jazz, Amgen</td>
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<td>Ownership interest (stock, stock options etc.)</td>
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<td>Expert testimony</td>
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<td>Other Relationships</td>
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Objectives

• Describe the basic etiology, pathophysiology and sequelae of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)
• List different treatment goals and options for AML and ALL
• Understand the mechanisms, efficacy and safety of newer targeted treatments
• Understand the role of cellular and stem cell therapy in treatment planning for AML and ALL
Polling Question: (Warm-up)

• How many leukemia patients have you encountered in your practice (acute leukemias such as acute myeloid leukemia or acute lymphoblastic leukemias, OR even chronic leukemias such as chronic lymphocytic leukemia or chronic myeloid leukemia)?
  A. None
  B. 1-5
  C. 5-10
  D. >10
Relative Incidence and Overview

- Common (class of) malignancy in children and adults
- Uncontrolled proliferation of immature malignant hematopoietic cells in the bone marrow
- 1 in 70 persons will develop leukemia in his/her lifetime
  - Prevalence > whites, males and increased age

Introduction to Hematopoiesis, Hematopoietic Stem Cells and the Bone marrow compartment

• Blood: the softest organ encapsulated by the hardest

• Normal hematopoiesis critical for survival
  • Red blood cell → oxygenation, CO₂ removal
  • Platelets → clotting
  • Innate and adaptive immune cells → fighting pathogens

• Hematopoietic stem cells (HSCs) are source of all blood cells
  • Live in the compartment of the (Red) Bone marrow
    • In adults, mostly in iliac crest and sternum
  • HSCs have a long life and can both
    • self-renew and
    • specialize (also called differentiation)

https://commons.wikimedia.org/wiki/File:Human_skeleton_front_arrows_no_labels.svg
Luis et al. Biological implications of clonal hematopoiesis. Exp Heme (2019); Aug (ahead of press)
Leukemia and Hematopoiesis

Myeloid

Common Myeloid Progenitor

- Megakaryoblast
- Proerythroblast
- Megakaryocyte
- Thrombocytes

Mast Cell

- Basophil
- Neutrophil
- Eosinophil

Red Blood Cells

Neutrophils

Lymphoid

Common Lymphoid Progenitor

- Lymphoblast
- Natural Killer Cell
- Small Lymphocyte
- B Lymphocyte
- T Lymphocyte
- Lymphoid Dendritic Cell

Multipotent Hematopoietic Stem Cell


Acute Leukemias by Mark Brown, PharmD Sep 2019
Differences and similarities between “solid organ” and “blood” malignancies

<table>
<thead>
<tr>
<th></th>
<th>Solid Tumours</th>
<th>Blood Tumours</th>
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<tbody>
<tr>
<td>Biology</td>
<td>Single cell (a “clone”) collects mutations and transforms</td>
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<tr>
<td>Presentation</td>
<td>Pain or discomfort, fatigue, a “lump”</td>
<td>Pain or discomfort, fatigue, a “lump” (lymph node) or aberrant CBC</td>
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<tr>
<td>Workup and diagnosis</td>
<td>“Tissue is the issue” Source organ</td>
<td>“Tissue is the issue” Lymph node or bone marrow</td>
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<td>Metastatic disease</td>
<td>Often = worse prognosis</td>
<td>Not a term used in hematology</td>
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<td>Treatment modalities</td>
<td>Surgery Drugs Radiation</td>
<td>Drugs Radiation</td>
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<td>Treatment drug groupings</td>
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<td>Traditional “cytotoxics” Immunotherapy Targeted therapies</td>
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<td>Treatment limitations</td>
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<td>Age and/or frailty</td>
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## Acute leukemias summarized

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<tr>
<th>Leukemia</th>
<th>Median age of diagnosis</th>
<th>Clinical Presentation</th>
<th>Special Lab Feature</th>
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<tr>
<td>Acute lymphoblastic leukemia (ALL)</td>
<td>14 (in adults, ~50)</td>
<td>• Children (75-100% ALL) -&gt; fever, lethargy, bleeding, enlarged liver or spleen, lymphadenopathy</td>
<td>Peripheral blasts</td>
</tr>
<tr>
<td>Acute myelogenous leukemia (AML)</td>
<td>67</td>
<td>• Adults (80% AML) -&gt; fever, fatigue, weight loss, SOB, chest pain, bleeding (nosebleeds, heavy menstruation)</td>
<td>Peripheral blasts and Auer rods</td>
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<tr>
<td>Acute promyelocytic leukemia (APL)</td>
<td>44</td>
<td>• As above but can present with coaguolopathies</td>
<td>T(15;17) (PML-RARA) chromosomal translocation</td>
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# Leukemias: treatment agents and survival, compared

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<tr>
<th>Leukemia</th>
<th>Representative Active Agent(s)</th>
<th>5-Yr Relative Survival Rate [CDN (2017)]</th>
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</table>
| Acute lymphoblastic leukemia (ALL)    | **Traditional cytotoxic chemotherapy:** many complex regimes<br>**Targeted therapy:** Blinatumumab, inotuzumab<br>**Cellular therapy:** Allogeneic stem cell transplant (Allo-SCT), Chimeric antigen receptor T-cell (CAR-T) therapy for <18 yrs | < 50 yrs: 75%  
≥ 50 yrs: 25% |
| Acute myelogenous leukemia (AML)      | **Traditional cytotoxic chemotherapy:** cytarabine, anthracyclines, etoposide, azacitidine/decitabine<br>**Targeted therapy:** Midostaurin<br>**Cellular therapy:** Allogeneic stem cell transplant (Allo-SCT) | < 50 yrs: 55%  
≥ 50 yrs: 14% |
| Acute promyelocytic leukemia (APL)    | **Traditional cytotoxic chemotherapy:** anthracyclines<br>**Targeted therapy:** All-trans-retinoic acid (ATRA, Vesanoid)<br>**Other:** Arsenic trioxide (ATO)<br>**Cellular therapy:** Allogeneic stem cell transplant (Allo-SCT) |  |

| Davis et al. AFP (2014); May 1(9):733 | NOT including acute promyelocytic leukemia (APL) – survival is VERY good in this subtype |


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Acute leukemias: Press down on the gas

• ”We have an ‘acute leuk’ coming in from OSH X…”
• **Not all “acute leukemics” are equally acute**
  • Often admission to hospital; “go to the hospital now” says the family/walk-in physician
• Rapid diagnosis paramount
• Assessment of tolerability critical
  • Pt will be offered options and risks
• Pts moved to front of all queues for preparation to receive intense therapy
  • Central line inserted for practical reasons—need to give a lot of drugs and IVF
• Treatment to start within 24-72 hours of admission
Acute lymphoblastic leukemia (ALL) and Acute myeloid leukemia (AML): hemato-pathogeneisis

• Characterized by rapid uncontrolled growth of immature lymphoid or myeloid cells ("blasts")
• Blasts crowd out bone marrow and spill into peripheral blood
  • Bone marrow failure and cytopenia(s) common → symptoms drive urgency
• Different cytogenetic and molecular subtypes are associated with different
  1. Prognoses (eg. Different levels of "badness")
  2. Treatments (eg. Different targeted drugs)
  3. Allogeneic stem cell "urgency" (eg. Should it be considered earlier or later)
• Diagnosis of type of acute leukemia (AML, ALL etc) critical; treatments VERY different

Mini-case: Acute leukemia Pt JH

• Pt is a 70 YOF
  • Social: Lives alone in Burlington; 1 daughter and retired from an accounting firm since 2011; nil smoking, EtOH or drug use
  • PMH: HTN and hyperlipidemia, both untreated
  • Meds levothyroxine 50 mcg PO daily

• Describes herself as being previously well until early Nov 2018 at which point she describes generalized weakness and fatigue
  • Dec 5 – developed dry cough and received a course of clarithromycin from a walk-in clinic
  • Dec 27 – Returned to walk-in clinic with cough and ongoing fatigue
    • CBC showing anemia and elevated WBC – referred to Dr. H hematologist in Burlington
  • Jan 3 – While awaiting an appointment, got a call from Dr. H – “Go to the Juravinski ED. I will as my colleague to admit you for further investigations and treatment.”
Polling Question

• What other conditions do you know of that can elevate the white blood cell count?
  A. Infection
  B. Systemic steroids eg. Prednisone PO
  C. Filgrastim (G-CSF)
  D. A polling question about leukocytosis
  E. A, B or C
Mini-case: Acute leukemia Pt JH

- On intake and history, Pt endorses
  - Generalized weakness for last 2-3 months
  - 20-30 pound Wt loss since Nov
  - 1 episode of drenching night sweats
  - Fever in ED – broad spectrum FN abx started (tazocin 4.5 grams IV q8h) – this is continued for over 1 month
# Mini-case: Acute leukemia Pt JH and CBC with differential (peripheral blood draw)

**Test** | **Result** | **Flag** | **Fusion Gene Transcript** | **Result**
--- | --- | --- | --- | ---
LKS | 106.4 | 5-10 x 10⁹/L | PML-RARA (Long, short, variable forms) | NOT DETECTED
CCS | 2.16 | | |
HCT | Not Done | | |
MCV | Not Done | | |
MCH | Not Done | | |
MCHC | Not Done | | |
RDW | Not Done | | |
**PLT** | 83 | 150-400 x 10⁹/L | |

**MANUAL DIFF.** | | | | |
**Absolute Neut** | 13.6 | H | 2.0-7.5 x10⁹/L | |
**Absolute Lymph** | 5.7 | H | 1.5-4.0 x10⁹/L | |
**Absolute Monos** | 31.2 | H | 0.2-0.8 x10⁹/L | |
**Absolute Blasts** | 52.7 | H | 0 x10 9/L | |
**Absolute Myelos** | 1.2 | | x10 9/L | |
**MORPHOLOGY** | | | | |
**LKS COMMENT** | See below | | | |
| MANY DEGENERATED (SMUGGED) CELLS NOTED Auer Rods | | | |
| Blasts on Scan | | | | |

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Leukemias – Pre-treatment Diagnosis/Diagnostics and Workup

1. “Tissue is the issue!”
   - Bone-marrow biopsy (BmBx)
     - Pathology stains for disease “markers”
       - Lymphoid → ALL protocols
       - Myeloid → AML protocols
   - Molecular tests (= quantitative PCR amplification)
     - Stain for drug targets
   - Cytogenetics (= anatomy of mutated chromosomes)
     - Stain for prognostication (badness of disease)

2. Imaging
   - Echocardiogram (“Echo”) to assess cardiac function

3. Chemistry/Other
   - CBC and chemistries for supportive care

4. Lumbar puncture and Cerebral Spinal Fluid (CSF) analysis
   - Always for ALL; sometimes in AML if there are CNS symptoms

Dx = diagnosis
Acute leukemias: Over-arching goals and principles of treatment

1. Treat now (or in the next 72 hours) and don’t wait too long
   • “Petal to the metal”
   • Treat with curative intent

2. Test for molecular markers
   • Some are now drug targets added as adjuncts
   • Some are for risk categorization

3. Begin work-up for allogeneic hematopoietic stem cell transplantation (allo-HSCT/allo-SCT)
   • Test family for a “match”

4. Support
   • Morbidity associated with disease
   • Treatment-related toxicity
Polling Question

• What do you imagine a “match” means?
  A. I don’t know, Bumble (or OKCupid, or Match, or Eharmony) figures that out!
  B. Match, like in matching for kidney or lung transplants
  C. Like, ”lighting the fire of urgency, man!” (said in a ”surfer”-esque tone)
  D. Why are you asking this? Ooooohhhh, you mentioned this on the last slide!
New terms, old terms: remission induction, consolidation and cure

• “Remission” or complete remission (used the same way)
  • Absence of measurable disease using standard diagnostic testing
    • Patient should be free of symptoms
    • Testing improving so ”moving target”
  • Complete remission #1 (CR1)
    • The first remission achieved with treatment after presentation

• ”Consolidation”
  • Intense treatment to kill off “un-measurable” disease (eg. sanctuary sites like testes, central nervous system)
    • (remember: these patients will be symptom-free)
  • High rates of early relapse without it

• Cure
  • Rarey officially declared; more of a hope—why we use “curative intent”
Acute Leukemia: A Simplified Treatment Pathway

- **Acute leukemia diagnosis**
  - **Very old / many co-morbidities** → Comfort care
  - **Lower risk** → Treat aggressively → Remission #1
  - **Higher risk** → Treat aggressively → Remission #1

- **Remission #1** → Wait (for relapse?) → Re-treat → Remission #2 → Allo-HSCT or other
Acute leukemias: Over-arching goals and principles of treatment

- **Presentation and Dx**
  - **AML**
    - Remission Induction
      - Consolidation x 1-4 cycles
        - Maintenance (+10 cycles)
    - ~1 month
  - **ALL**
    - Remission Induction
      - Consolidation X 1-4 cycles
        - Maintenance (+10 cycles)
    - ~1 month

~2 years
Acute leukemias: Over-arching goals and principles of treatment

**Presentation and Dx**

- **AML**
  - Remission Induction
  - Consolidation x 1-4 cycles
  - Maintenance (+10 cycles)
  - ~1 month

- **ALL**
  - Remission Induction
  - Consolidation X 1-4 cycles
  - Maintenance
  - ~1 month
  - ~2 years

Patient may have 1 or more low blood counts at presentation but ALL counts will go VERY low during induction.
Polling Question

• If you treat any cancer patients in your current practice, what kinds of CBC parameters (ie. “counts”) might prevent treatment with the next on-schedule cycle of chemotherapy?
  A. Normal counts (hemoglobin, WBC and neutrophils and platelets) or there will be a delay.
  B. Slightly depressed counts are ok, depending on the trend
  C. We will treat patients with chemotherapy even if one or more of the main lineages (Hgb, WBC or platelets) are low
Acute Lymphoblastic Leukemia (ALL)
Incidence and Risk Factors

• Incidence and distribution
  • 80% of childhood leukemias and 20% of adult leukemias
  • Bimodal distribution – first peak at 5 years, second ~50 years old
    • 60% of Pts diagnosed younger than 20;
    • ~10% ≥ 65 years

• Risk factors
  • Age
  • Exposure to chemotherapy or radiation
  • Genetic disorders esp. Down syndrome (Trisomy 21)
Acute Lymphoblastic Leukemia (ALL)  
Differential Diagnosis and Prognoses

• Bone marrow biopsy
  • high % malignant lymphoblasts in bone marrow and peripheral blood
  • Many sub-types
    • Pre-cursor B-cell ALL, mature B-cell ALL and T-cell ALL

• Prognostic factors
  • Favourable
    • Younger age
    • Low WBC
    • Early achievement of complete remission (CR)
  • Unfavourable
    • Older age, high WBC,
    • Philadelphia chromosome (BCR-ABL) positivity aka “Ph+”, t(4;11), t(8;14), complex cytogenetics
BCR-ABL (Philadelphia chromosome+) ALL and role of allo-HSCT

• BCR-ABL/Philadelphia chromosome+ aka Ph+ ALL
  • The reciprocal translocation b/t chromosomes 9 & 22 = t(9;22)
    • Leads to formation of oncogene BCR-Abl kinase –
      • Apoptosis avoidance and increased proliferation
  • ~25% adults (~3% in children)
  • Historically patients to receive an allogeneic stem cell transplant early in their therapy
    • Tyrosine kinase inhibitors (TKIs) imatinib, dasatinib or ponatinib given in combination with traditional protocols drastically improves responses

Dx = diagnosis
## Acute Lymphoblastic Leukemia (ALL): Treatment Options

<table>
<thead>
<tr>
<th>Traditional Cytotoxic Agents</th>
<th>Biologics</th>
<th>Complex Regimes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide (<strong>alkylator</strong>)</td>
<td>Rituximab (Rituxan; anti-CD20)</td>
<td>Allogeneic Stem Cell Transplant (Preparative regimes)</td>
</tr>
<tr>
<td>Vincristine (<strong>vinca alkyloid</strong>)</td>
<td>Blinatumomab (Blincyto; BITE-CD19/3)</td>
<td>Chimeric Antigen Receptor T-cell Therapy (CAR-T)</td>
</tr>
<tr>
<td>Doxorubicin (<strong>anthracycline</strong>)</td>
<td>Inotuzumab ozogamicin (Besponsa; anti-CD22)</td>
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<tr>
<td>Daunorubicin (<strong>anthracycline</strong>)</td>
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<tr>
<td>Cytarabine (HD-IV,IT) (<strong>DNA synthesis-I</strong>)</td>
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<tr>
<td>Methotrexate (HD-IV,LD-IV,IT; anti-metabolite)</td>
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<tr>
<td>6-mercaptopurine (<strong>6-MP</strong>) (anti-metabolite)</td>
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<thead>
<tr>
<th>Enzymes (actively deplete asparagine)</th>
<th>Tyrosine Kinase Inhibitors (Ph+ only)</th>
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<tbody>
<tr>
<td>L-Asparaginase</td>
<td>Imatinib (Gleevec)</td>
</tr>
<tr>
<td>PEG-Asparaginase (<strong>Oncospar</strong>)</td>
<td>Dasatinib (Sprycel)</td>
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<td>Nilotinib (Tasigna)</td>
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<td>Ponatinib (Iclusig)</td>
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<tr>
<th>Miscellaneous</th>
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<tbody>
<tr>
<td>Corticosteroids (prednisone and dexamethasone)</td>
<td>Complex Regimes</td>
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Acute Leukemias by Mark Brown, PharmD Sep 2019
### Acute lymphoblastic leukemia (ALL): Upfront therapy

<table>
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<tr>
<th>Initial</th>
<th>Guideline Recommended Regimens</th>
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<tbody>
<tr>
<td><strong>Induction treatment</strong></td>
<td>Multi-agent chemotherapy (usually from multi-institutional cooperative group studies. Names like CALGB, COG, DFCI) Most include: anthracycline (doxorubicin or daunorubicin), vincristine, high dose steroids, pegasparaginase +/- HD-MTX OR +/- cyclophosphamide</td>
</tr>
<tr>
<td><strong>IF Ph+ (BCR-ABL+)</strong></td>
<td>Add to multi-agent chemotherapy: Imatinib OR dasatinib OR nilotinib OR ponatinib (continues through consolidation &amp; maintenance below)</td>
</tr>
<tr>
<td><strong>Consolidation and maintenance</strong></td>
<td>Similar agents to induction but with less intensity</td>
</tr>
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Acute Lymphoblastic Leukemia (ALL): Principles of Treatment

- All children treated on a clinical trial
- Adults received slightly watered-down multi-agent children protocols
  - Applying children-protocol intensity to adults = improved survival
    - Exception for elderly (≥65 years)
  - Multi-agent traditional chemotherapy
    - + whole-brain radiation (for Pts with CNS+ disease; ~10% of Pts at presentation)
    - + Tyrosine kinase inhibitor (TKI; for Ph(+) ALL)
- Consideration for allo-HSCT (or CAR-T for ages 3-25 in Canada)
  - High risk cytogenetics and/or many poor prognostic factors OR
  - Relapse/refractory disease eg. Treat in 2\textsuperscript{nd} complete remission (CR2)
Acute Lymphoblastic Leukemia (ALL): Principles of Treatment

- Treatment is highly complex
  - 3 main phases
    1. **Remission Induction** treatment (~1 month)
       - Steroid (prednisone) backbone
    2. **Consolidation** phase (several months)
       - Agents: Dexamethasone, vincristine, 6-mercaptourine (6-MP), doxorubicin or methotrexate, asparaginase
    3. **Maintenance** phase (outpatient; ~2 years)
       - Agents: Dexamethasone, vincristine, 6-mercaptourine (6-MP), doxorubicin or methotrexate, asparaginase
  - **Central Nervous System (CNS) treatment**
    - Whole-brain radiation for patients presenting with CNS disease (~10%)
    - CNS chemotherapy prophylaxis for everyone

- Many routes for chemotherapy
  - IV, IM, PO, IT
  - ALL receive intrathecal therapy (IT) as prophylaxis
    - ~75% will develop CNS disease after 1 year if they don’t receive this
## Remission Induction for ALL (Modified Dana-Farber Cancer Institute (DFCI protocol)

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<tr>
<td>Vincristine (IV)</td>
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<td>Doxorubicin (IV)</td>
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<td>HD-Methotrexate (IV) (eg 4000 mg/m2)</td>
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<td>Leucovorin (IV) (to rescue from MTX)</td>
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<td>Prednisone (PO)</td>
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<td>Peg-Asparaginase (IV/IM)</td>
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<td>Lumber puncture</td>
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<td>Cytarabine (IT)</td>
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<td>Bone Marrow bx</td>
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</tbody>
</table>
# Acute lymphoblastic leukemia (ALL): Relapse and refractory

<table>
<thead>
<tr>
<th>Initial</th>
<th>Guidelined recommended Regimens</th>
<th>Alternative Regimens</th>
</tr>
</thead>
</table>
| Relapse refractory | Blinatumomab (B-ALL)  
Inotuzumab ozogamicin (B-ALL)                                           | **Reinduction** multi-agent chemo:  
Hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, vincristine, dexamethasone, high-dose methotrexate, high-dose cytarabine) |

| IF Ph+ (BCR-ABL+)    | Add to multi-agent chemotherapy:  
Imatinib OR dasatinib OR nilotinib OR ponatinib                           |                                                                                       |
Inotuzumab ozogamicin (IO; Besponsa)

- CD22 highly expressed on B-cells
- Inotuzumab ozogamicin is monoclonal Antibody Drug Conjugate (ADC) bound to calicheamicin
  - Calicheamicin is a tubulin binding toxin that also binds DNA causing double strand breaks


Acute Leukemias by Mark Brown, PharmD Sep 2019
Inotuzumab ozogamicin VS standard intensive chemotherapy for relapse/refractory ALL (INO-VATE)

- **Rationale and background**
  - Adults with ALL have cure rates ~40%; means many will relapse
  - 5-year OS of relapse/refractory of adult ALL <10%
  - With standard intensive chemotherapy, ~40% with achieve remission (CR2); dismal

- **Design**
  - Randomized, open-label, two-group, phase III for Pts 18 years or older with relapse or refractory CD22 ALL

  ![Study Design](chart)

  - **Primary**: Complete remission (CR[2]), including complete remission with incomplete hematologic recovery AND OS. Secondary: Safety, duration of remission, PFS, rate of subsequent allo-HSCT

  Kantarjian et al. NEJM (2016);375(8):740 | * NO cross-over was allowed; any Pt achieve remission could go on to all-HSCT |
  Investigator’s choice of standard therapy = FLAG (fludarabine, cytarabine, GCSF), OR cytarabine/mitoxantrone OR high-dose cytarabine

  Acute Leukemias by Mark Brown, PharmD Sep 2019
Inotuzumab ozogamicin VS standard intensive chemotherapy for relapse/refractory ALL (INO-VATE)

<table>
<thead>
<tr>
<th></th>
<th>IO (n=109)</th>
<th>Std Chemo (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=218</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>47 (18-78)</td>
<td>27 (18-79)</td>
</tr>
<tr>
<td>CR (as treated)*</td>
<td>80.7% (95CI, 72-88)</td>
<td>29.4% (95CI, 21-39)</td>
</tr>
<tr>
<td>OS</td>
<td>7.7 (NS)</td>
<td>6.7 (NS)</td>
</tr>
<tr>
<td>Allo-HSCT in CR2</td>
<td>41%</td>
<td>11%</td>
</tr>
</tbody>
</table>

### Duration remission

- **Probability of Remaining in Remission**
  - Inotuzumab ozogamicin group
  - Standard-therapy group

### Overall survival

- **Probability of Overall Survival**
  - Inotuzumab ozogamicin group
  - Standard-therapy group

Kantarjian et al. NEJM (2016);375(8):740 | Was to be intent-to-treat, but 13/109 Pts in Std therapy arm refused treatment altogether
Canadian Monograph, accessed Aug 2019
Acute Leukemias by Mark Brown, PharmD Sep 2019
Inotuzumab ozogamicin VS standard intensive chemotherapy for relapse/refractory ALL (INO-VATE)

- IO superior to standard therapy in terms of complete remissions
- OS in question. Authors claim statistical assumptions maybe responsible
- Questions remain about best post-remission strategy
- Veno-occlusive disease (VOD) a major concern for Pts eligible for transplant

<table>
<thead>
<tr>
<th>Toxicity (Gr 3/4)</th>
<th>IO</th>
<th>Std Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Veno-occlusive disease (VOD)</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>VOD among allo-HSCT*</td>
<td>22%</td>
<td>(not reported)</td>
</tr>
</tbody>
</table>

Kantarjian et al. NEJM (2016);375(8):740 | Mori et al. Letter to Editor, NEJM (2016);375;21:3100 | *Analysis by study group showing that dual-alkylator was strongest associate co-variate for VOD
Acute Lymphoblastic Leukemia (ALL): Supportive Care Issues

• Tumour lysis syndrome (TLS) management, especially during first days of induction
  • Aggressive IVF, allopurinol for hyperuricemia and/or rasburicase

• Febrile neutropenia and infection (this WILL happen)
  • Broad spectrum antibiotics common including penicillins (eg. tazocin), carbapenems (meropenem), -azole and echinocandin antifungals (eg. fluconazole and caspofungin, respectively)
  • PJP propylaxis until chemo stops

• Transfusions of red blood cells and platelets are very common during induction
Polling Question

• What do you know to be, or would guess to be the best clinical indicator of a patient with an infection related to their leukemia or treatment of their acute leukemia?
  A. A positive blood or urine culture from the patient
  B. Fever
  C. Symptoms of sepsis, including fever, hypotension, and positive microbial cultures
  D. Leucocytosis
Acute Lymphoblastic Leukemia (ALL): Supportive Care Issues

- Treatment-related toxicity
  - Steroid management
    - Steroid-induced DM, psychosis/mood
    - Longer/intermediate-term avascular necrosis/osteonecrosis, myopathy, weight-gain
    - Steroid-induced hyperglycemia
  - Neuropathies due to vinca alkaloid (vincristine) treatment
    - Peripheral sensory common and can be irreversible (eg. Neuropathic pain, foo—drop)
  - Thrombosis
    - ADR associated with asparaginase AND central venous access device (CVAD) use
- Survivorship issues, particular for younger patients
  - Risk of relapse
  - Secondary cancers in older age

Hallek M et al. Blood 2008;111:5446
AML

Acute myeloid (myelogenous) leukemia (AML)
Acute Myeloid Leukemia (AML)
Incidence and Risk Factors

• Incidence and distribution
  • Median age at diagnosis is ~70;
  • Of estimated 18,860 cases in 2014, 10,460 will die of the disease

• Risk factors
  • Age (>70 years)
  • Ethnic origin: USA/Canada/Europe > Japan/China (retained if emigration)
  • Petrochemicals such as benzene, pesticides, ionizing radiation
  • Exposure to chemotherapy (eg secondary AML) (*worse prognosis)
    • Alkylators (eg. cyclophosphamide, melphalan), topoisomerase-inhibitors (eg. etoposide, doxorubicin, mitoxantrone)
  • Radiation, particularly treatment-related (eg. total-body irradiation)


Acute Leukemias by Mark Brown, PharmD Sep 2019
Outcomes in AML Therapy

• Before the 1960s, AML “incurable”

• CR rates to 70-80%

• 5-year disease free survival range from 25-30%
  • “Cure” defined by death by age-matched non-AML Pts happens though data is variable

• Differences between young and older AML patients persists

Mrozek et al. JCO (2012); Vol 30(36):4515
Acute Myeloid Leukemia (AML)
Differential Diagnosis and Prognoses

• Clinical presentation same as with ALL

• Bone marrow biopsy
  • high % malignant myeloblasts in bone marrow and peripheral blood

• Prognostic factors
  • Cytogenetics and molecular markers confer prognosis “level”
    • Good prognosis
    • Intermediate prognosis
    • Poor prognosis
      • Eg. FLT3(+) molecular mutation
        • 5 year survival rate 15% with treatment, 78% relapse rate
Acute myeloid Leukemia (AML): Principles of Treatment

- Treatment is highly complex
- 3 main phases
  1. Remission Induction treatment (~1 month)
     - Cytarabine and anthracycline are backbone
  2. Consolidation phase (several months)
     - More cytarabine, sometimes anthracycline
  3. Maintenance phase (outpatient; ~2 years)
     - N/A
- Central Nervous System (CNS) treatment
  - Whole brain radiation for patients presenting with CNS disease (~10%)
  - CNS chemotherapy prophylaxis for everyone
- Many routes for chemotherapy
  - IV, IM, PO
  - Intrathecal therapy (IT) as prophylaxis (~75% will develop CNS disease after 1 year if they don’t receive this)
# Acute Myeloid Leukemia (AML): “Agents” Used in its Treatment

<table>
<thead>
<tr>
<th>Traditional Cytotoxic Agents</th>
<th>Differentiating Agents (APL sub-type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarubicin (anthracycline)</td>
<td>All-trans-retinoic acid (ATRA)</td>
</tr>
<tr>
<td>Daunorubicin (anthracycline)</td>
<td>Arsenic Trioxide</td>
</tr>
<tr>
<td>Cytarabine (HD-IV,IT) (DNA synthesis-I)</td>
<td>Hypomethylating agents</td>
</tr>
<tr>
<td>Liposomal</td>
<td><strong>Azacitidine</strong> (Vidaza)</td>
</tr>
<tr>
<td>Mitoxantrone (anthracedione)</td>
<td>Decitabine (Dacogen; SAP)</td>
</tr>
<tr>
<td>Etoposide (topoisomerase-I)</td>
<td></td>
</tr>
<tr>
<td>Fludarabine (purine analog)</td>
<td></td>
</tr>
<tr>
<td>Clofarabine (purine analog)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Targeted agents</th>
<th>Hypomethylating agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Midostaurin</strong> (Rydapt; FLT3+-I)</td>
<td><strong>Azacitidine</strong> (Vidaza)</td>
</tr>
<tr>
<td></td>
<td>Decitabine (Dacogen; SAP)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complex Regimes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allogeneic Stem Cell Transplant</strong> (Preparative regimes)</td>
</tr>
</tbody>
</table>

Acute Leukemias by Mark Brown, PharmD Sep 2019
# Acute myeloid leukemia (AML): Upfront therapy

<table>
<thead>
<tr>
<th>Stage of treatment</th>
<th>Guideline Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction treatment (AML)</td>
<td>“7+3”</td>
</tr>
<tr>
<td></td>
<td>Cytarabine continuous infusion (7 days)/ Idarubicin OR daunorubicin as IV boluses daily for 3-4 days</td>
</tr>
<tr>
<td></td>
<td><strong>If FLT3+ mutation, add to above</strong></td>
</tr>
<tr>
<td></td>
<td>Midostaurin PO days 8-21 to above induction therapy</td>
</tr>
<tr>
<td>Induction treatment (Acute promylocytic leukemia (APL))</td>
<td>Arsenic trioxide IV/All-trans retinoic acid PO/ +/- idarubicin</td>
</tr>
<tr>
<td>Consolidation</td>
<td>High-dose cytarabine “7+3” x 1 (for 2 total) then high-dose cytarabine</td>
</tr>
<tr>
<td></td>
<td><strong>If FLT3+ mutation, add to above</strong></td>
</tr>
<tr>
<td></td>
<td>Midostaurin PO days 8-21 to above consolidation therapy</td>
</tr>
<tr>
<td>Re-induction (for relapse and refractory)</td>
<td>Can use above regimesFLAG-IDA, age-adjusted (Fludarabine/ cytarabine/ GCSF/ idarubicin)</td>
</tr>
<tr>
<td></td>
<td>*in context of relapse, goal is remission → allo-HSCT</td>
</tr>
</tbody>
</table>

| NCCN Practice Guidelines Acute myeloid leukemia V.1.2019 |

Acute Leukemias by Mark Brown, PharmD Sep 2019
Mini-case: Acute leukemia Pt JH

- Jan 6
  - Pt is started on 7+3
- Jan 20
  - Pt admitted to ICU for respiratory failure
- Jan 23
  - Intubated; BAL tested positive for RSV and aspergillosis
  - Pt started on amphotericin
- Jan 27
  - Counts begin to recover
  - Renal failure
- Feb 10th
  - Continued to require 100% O2
  - Comfort measures and passed away

**Molecular Oncology Results**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1</td>
<td>Exon 12</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>FLT3-ITD</td>
<td>Juxtanembrane domain</td>
<td>POSITIVE</td>
</tr>
</tbody>
</table>

**14-day course midostaurin**
Acute Myeloid Leukemia (AML): Relapse and refractory

• Pts who are refractory or relapsed will treated with “more of the same” to re-establish remission
  • For refractory (ie. Not responding to initial remission induction therapy), hope is a stubborn CR1 then “straight to transplant”
  • For relapsed, (what were lower risk Pts), goal is to induce a second remission (CR2) then ”straight to transplant”
    • This can be months to years from original induction
    • Age can become a major barrier to toxic treatment
Acute Myeloid Leukemia (AML): Supportive Care Issues

• Tumour lysis syndrome (TLS) management, especially during first days of induction
  • Aggressive IVF, allopurinol for hyperuricemia and/or rasburicase

• Febrile neutropenia and infection (this WILL happen)
  • Broad spectrum antibiotics common including penicillins (eg. tazocin), carbapenems (meropenem), -azole and echinocandin antifungals (eg. fluconazole and caspofungin, respectively)
  • PJP propylaxis until chemo stops

• Transfusions of red blood cells and platelets are very common during induction

Hallek M et al. Blood 2008;111:5446
Role of cellular therapy (Allogeneic stem cell transplant and Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

- **Allogeneic hematopoietic stem cell therapy (Allo-HSCT)**
  - Donor is other than "self" (similar to liver, kidney, lung transplant etc)
  - Often only chance at cure for acute leukemias
    - Treatment-related mortality @ 2 years ~30% (1 in 3 will die due to complications of procedure)
  - Allo-HSCT offered early for poor risk acute leukemia

- **Chimeric antigen receptor T-cell (CAR-T) therapy**
  - Genetic modification of patient’s T-cell therapy against ALL marker CD19
  - Tisagenlecleucel (Kymriah) for ages 3-25
    - N=75 Pts, 60% remission rates in treatment-refractory patients
Leukemias Conclusions and Wrap-Up

• ALL
  • Disease of pediatrics primarily
  • Potentially curable with standard therapy, but rapidly fatal if not treated
  • Induction + consolidation + maintenance
  • Allo-HSCT, CAR-T for younger patients

• AML
  • Durable remissions possible, but rapidly fatal if not treated
  • Induction + consolidation
  • Allo-HSCT