T-cell ALL
Clinical Case

- 48 year old woman
- May 2015
  - Presents to OSH in AZ with fatigue, sweats, abdominal pain, easy bruising

12.1  29  30  0.6

Circulating 5% blasts

AST 142
ALT 221
Alk phos 1000
LDH 733
Lymphoblast vs. Myeloblast

**Lymphoblast**
- Smaller
- Round nucleus
- Scanty cytoplasm

**Myeloblast**
- Larger
- Round, oval or irregular nucleus
- Lots o’ cytoplasm
- Granules
- Auer rods!
Case, continued

• Bone marrow bx w/95% involvement
  – Cells express CD3, CD5 and CD7 along with CD56
T-cell acute lymphoblastic leukemia
ALL Incidence By Age

Data from SEER, reported in Dores et al Blood 2012
ALL Relative Survival

Data from SEER, reported in Dores et al Blood 2012
<table>
<thead>
<tr>
<th>Presentation of T-ALL</th>
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</table>

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median 26.6, range 14-52</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>75% male</td>
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<tr>
<td><strong>WBC count</strong></td>
<td>Median 48K, range 0.5-84</td>
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<tr>
<td><strong>Hb</strong></td>
<td>Median 10.8, range 5-17</td>
</tr>
<tr>
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<td><strong>Lymphadenopathy</strong></td>
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<tr>
<td><strong>Splenomegaly</strong></td>
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<td><strong>Mediastinal mass</strong></td>
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<td>(kidney, skin, testis)</td>
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Common
## Presentation of T-ALL

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<th>Characteristic</th>
<th>Details</th>
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T-ALL vs. T-LL

T-ALL
- >20% marrow blasts

T-cell lymphoblastic lymphoma
- <20% marrow blasts
Subtypes of T-ALL

**Table 1. Immunologic classification of T-ALL**

<table>
<thead>
<tr>
<th></th>
<th>cCD3</th>
<th>CD7</th>
<th>CD28</th>
<th>CD1a</th>
<th>CD34</th>
<th>CD4</th>
<th>CD8</th>
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<tbody>
<tr>
<td>Pro-T</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Pre-T</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cortical T</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Mature T* (medullary)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

cCD3, cytoplasmic CD3.

*Also surface (membrane) CD3⁺.
Early T-cell Precursor (ETP) ALL

Early: cell surface antigen profile consisting of lack of CD1 and CD8, weak CD5, and the expression of at least one myeloid- or stem cell–related marker

Data from van Vlierberghe et al, Blood, 2013
Genetic Mutations in ALL

Litzow MR and Ferrando AA, Blood, 2015
Four gene classifier

Mutation in either NOTCH or FBXW7 AND Wild-type RAS and PTEN

Triquand et al JCO 2013
Lepretre et al JCO 2016
T-ALL, treatment

Newly Diagnosed T-ALL

- Suitable for pediatric-intensive chemotherapy
  - Pediatric-intensive multi-agent chemotherapy regimen
    - CR
      - MRD negative/no adverse genetics*
        - Observe
      - MRD positive and/or adverse genetics*
        - Consolidation / Maintenance Chemotherapy
    - No CR
      - Neralabine/clinical trial/other salvage chemotherapy

- Not suited for pediatric-intensive chemotherapy (older age, co-morbidities)
  - Conventional multi-agent chemotherapy
    - No CR
      - MRD positive and/or adverse genetics**
        - Observe
      - MRD negative/no adverse genetics**
        - Consolidation / Maintenance Chemotherapy
    - CR
      - Allogeneic SCT (MA or RIC)

Litzow MR and Ferrando AA, Blood, 2015
T-ALL, treatment

Key decision point = pediatric versus not

Litzow MR and Ferrando AA, Blood, 2015
Pediatric regimens: T-cell ALL

Abdelali et al, Blood, 2011
Huguet et al, JCO, 2009
### Pediatric induction

#### Remission Induction Therapy (Course I) (see Section 7.2) (see Section 7.1.5 for infection prophylaxis)

<table>
<thead>
<tr>
<th></th>
<th>IT</th>
<th>Ara-C</th>
<th>Prednisone Days 1-28</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allopurinol</strong></td>
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<tr>
<td></td>
<td>Allopurinol 300 mg/day (unless allergic) to continue until peripheral blasts and extramedullary disease are reduced.</td>
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<tr>
<td><strong>IT-Ara-C</strong></td>
<td>Ara-C 70 mg IT on Day 1. <strong>IT ara-C may be given prior to registration for patient convenience at the time of diagnostic bone marrow or venous line placement to avoid a second lumbar puncture.</strong></td>
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<tr>
<td><strong>Pred</strong></td>
<td>Prednisone 60 mg/m²/day PO or IV (methylprednisolone) in two divided doses on Days 1-28. <strong>Do not taper.</strong></td>
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<tr>
<td><strong>VCR</strong></td>
<td>Vincristine 1.5 mg/m² (maximum 2 mg) IV on Days 1, 8, 15, and 22. Voriconazole and posaconazole are contraindicated with vincristine.</td>
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<tr>
<td><strong>DNR</strong></td>
<td>Daunorubicin 25 mg/m² IV on Days 1, 8, 15, and 22.</td>
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<tr>
<td><strong>PEG</strong></td>
<td>PEG-asparaginase 2500 IU/m² IM or IV x 1 dose on Day 4 (OR Day 5 OR Day 6). Premedicate with 650 mg acetaminophen, 100 mg hydrocortisone and 25-50 mg diphenhydramine (or equivalent) prior to PEG-asparaginase.</td>
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<tr>
<td><strong>IT-MTX</strong></td>
<td>Methotrexate 15 mg IT on Day 8 and Day 29.</td>
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<tr>
<td><strong>(*) BM</strong></td>
<td><strong>For patients with CNS3 disease, IT-MTX is also administered on Day 15 and 22.</strong></td>
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<tr>
<td><strong>BM</strong></td>
<td>Bone marrow aspirate and biopsy specimen must be obtained for all patients on Day 15 to assess initial response, and on Day 29 to assess induction response and minimal residual disease (see Section 7.9.2).</td>
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<tr>
<th>Day</th>
<th>1</th>
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<th>22</th>
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</table>

**CALGB 10403**
Pegasparaginase

- ALL cells need asparagine
- ALL cells cannot synthesize enough asparagine
- Pegasparaginase enzymatically depletes asparagine

Patient drawing of pegasparaginase from http://chemosabe-socks.blogspot.com
Pegasparaginase

I like to say in talks that it took an article of 20+ pages to summarize the management of side-effects of asparagine depletion in adults.
Pegasparaginase

% Adults with Grade 3/4 toxicity

- Elevated LFTs
- Hypofibrinogenemia
- Thrombosis
- Bleeding
- Elevated INR
- Pancreatitis
- Hyperglycemia
- CNS ischemia
- Neuropathy
- Fatigue
- Nausea

Stock et al, Leuk Lymphoma, 2011
Pegasparaginase

- Low fibrinogen = common
- Thrombosis = common
- Bleeding = rare

- Let the fibrinogen run low!!!
Standard regimens

- Hyper-CVAD
- Others
Back to our case

• Starts hyper-CVAD
  – Blasts resolve, lymphadenopathy improves, symptoms improve

• CNS tap - + for malignancy
  – Ommaya placed
  – IT chemo w/MTX -> seizure
  – IT chemo w/ara-C for several months
Presentation to UWMC

- Patient presented w/new onset left sided hemiparesis
- CNS tap, peripheral blood at presentation initially negative
- Starts circulating blasts
- Repeat Ommaya tap +
- MRI with nerve root involvement
Salvage regimens

• Nelarabine
  – Prodrug for ara-G
  – Phase II study in relapsed T-ALL
    • 41% response rate, 31% CR
    • Median remission of 20 weeks
    • Some very long responses
    • Side effects: fatigue, weakness, GI upset, cytopenias

DeAngelo et al, Blood, 2007
Case

• Discussion between med onc, rad onc, neuro-onc
• Patient received 2 doses Ara-C to temporize, then receives cycle of nelarabine
• Also receives radiation therapy to brachial plexus and sacral plexus
• Also receives IT cytarabine
Case, continued

• Patient responds well
  – Regains strength in left arm
  – Regains ability to walk a few steps (with walker)
  – No major treatment related adverse events
Clinical trials

- Many fewer trials for T-ALL
- Phase I/II at UWMC: UW15024
  - Oral inhibitor of BET

 Trial drug from incyte
Schematic from tensha therapeutics
Thank you

Dr. Ryan Cassaday discusses options for treating ALL.

Play video
Thank you all for your attention

Image by Scott Adams
From www. Forbes.com