Adult T-cell lymphoblastic leukemia/lymphoma
Lymphoma Tumor Board
April 28, 2017
## WHO / Revised European American Lymphoma (REAL) Classification

<table>
<thead>
<tr>
<th>B-cell lymphomas (80% - 85%)</th>
<th>T-cell lymphomas (15% - 20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diffuse large B-cell lymphoma</td>
<td>• Precursor T-lymphoblastic lymphoma/leukemia</td>
</tr>
<tr>
<td>• Follicular lymphoma</td>
<td>• Peripheral T-cell lymphomas</td>
</tr>
<tr>
<td>• Chronic lymphocytic leukemia / small lymphocytic lymphoma</td>
<td>• Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome, and others)</td>
</tr>
<tr>
<td>• Mantle cell lymphoma</td>
<td>• Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>• Marginal zone B-cell lymphomas</td>
<td>• Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>• Burkitt lymphoma</td>
<td>• Extranodal natural killer/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>• Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)</td>
<td>• Enteropathy-associated intestinal T-cell lymphoma (EATL)</td>
</tr>
<tr>
<td>• Hairy cell leukemia</td>
<td>• Anaplastic large cell lymphoma (ALCL)</td>
</tr>
<tr>
<td>• Primary central nervous system (CNS) lymphoma</td>
<td>• Peripheral T-cell lymphoma, unspecified</td>
</tr>
</tbody>
</table>
Diagnosis of T-cell lymphoblastic leukemia/lymphoma

- Lymphoblastic lymphoma (LBL) is rare
- Sub-type of lymphoma that is generally of T-cell origin
- Comprises about 2% of all NHLs in adults
- Characteristics are very similar to acute lymphoblastic leukemia (ALL)
- Patients with predominantly nodal disease at presentation are classified as LBL, whereas those with primarily disease in the marrow or peripheral blood are classified as ALL
- Historically, no standard of care treatment specifically designed for LBL
- Pathology – antigens usually evaluated at time of diagnosis:
  - CD45 (LCA), CD3, CD2, CD5, CD7, TdT, CD1a, CD10, CD19, CD20, CD79a, kappa/lambda, CD13, CD33, myeloperoxidase
Classification of ALL

ALL – CLASSIFICATION
WHO

- Uses immunophenotypic classification:
  - Acute lymphoblastic leukemia/lymphoma (Former Fab L1/L2)
  - Precursor B acute lymphoblastic leukemia/lymphoma.
    - Cytogenetic subtypes:
      - t(12;21)(p12,q22) TEL/AML-1
      - t(1;19)(q23;p13) PBX/E2A
      - t(9;22)(q34;q11) ABL/BCR
      - T(V,11)(V;q23) V/MLL
  - Precursor T acute lymphoblastic leukemia/lymphoma
  - Burkitt’s leukemia/lymphoma (Former FAB L3) (mature B cell ALL)
  - Biphenotypic acute leukemia (2 to 5%)
Pathology of T-cell lymphoblastic leukemia/lymphoma

**Image A.** T-cell lymphoblastic lymphoma/leukemia in bone marrow biopsy. Neoplastic lymphocytes surround residual megakaryocytes and erythroid precursors. H&E section of formalin fixed tissue.

**Image B.** T-cell lymphoblastic lymphoma/leukemia. Cytology of lymphoblasts reveals medium sized cells with delicate unclumped chromatin, convoluted nuclear membrane and small but distinct nucleoli.
Immunophenotype of T-cell leukemia/lymphoma

Table 1. T-cell CD antigen expression in pro-, pre-, cortical (thymic), and mature T-cell ALL cyCD3 indicates cytoplasmic CD3; sCD3, surface CD3

<table>
<thead>
<tr>
<th></th>
<th>cyCD3</th>
<th>CD7</th>
<th>CD5</th>
<th>CD2</th>
<th>CD1a</th>
<th>sCD3</th>
<th>CD34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-T</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>±</td>
</tr>
<tr>
<td>Pre-T</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>—</td>
<td>—</td>
<td>±</td>
</tr>
<tr>
<td>Cortical (thymic)</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>—</td>
</tr>
<tr>
<td>Mature</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>—</td>
<td>+</td>
<td>—</td>
</tr>
</tbody>
</table>
The landscape of genetic alterations in T-ALL

Mark R. Litzow, and Adolfo A. Ferrando Blood
2015;126:833-841

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Deregulation of the JAK-STAT signaling cascade in T-ALL

Representation of the cooperation of oncogenic events

ALL: TYPICAL TREATMENT

• Primary objective: to achieve and maintain a complete remission (CR)
• Induction, consolidation, maintenance phases
  • CNS prophylaxis with IT-MTX during induction and consolidation phases

CNS Prophylaxis (IT-MTX) → Induction → Consolidation → Maintenance

Over a period of months
2-3 years
Treatment of T-cell lymphoblastic leukemia/lymphoma

- Adaptation of pediatric protocols of intensive chemotherapy and CNS prophylaxis has led to marked improvements in outcomes in adults
- Numerous chemotherapy/radiotherapy regimens are similar in dose and schedule to ALL regimens
- Common features of these regimens include:
  - Induction therapy
  - CNS prophylaxis
  - Consolidation therapy
  - Subsequent maintenance therapy for 12 to 18 months
- Long-term disease-free survival rates between 40-70%
# Treatment

## Table 1

### Intensive Induction Regimens for Adult Lymphoblastic Lymphoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>N</th>
<th>Response Rate</th>
<th>Failure-Free Survival/Relapse-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman et al [11]</td>
<td>Two ALL-type protocols with intensified CNS</td>
<td>44</td>
<td>100%</td>
<td>3-yr FFS = 56%</td>
<td>NA</td>
</tr>
<tr>
<td>Slater et al [12]</td>
<td>Various ALL protocols</td>
<td>51</td>
<td>80% CR for “nonleukemic”; 77% CR for leukemic</td>
<td>NA</td>
<td>5-yr actuarial OS = 45%</td>
</tr>
<tr>
<td>Bernasconi et al [13]</td>
<td>Various ALL protocols</td>
<td>31</td>
<td>77% OR</td>
<td>3-yr RFS = 45%</td>
<td>3-yr OS = 59%</td>
</tr>
<tr>
<td>Levine et al [16]</td>
<td>Modified LSA₁L₂</td>
<td>15</td>
<td>73% CR; 27% PR</td>
<td>5-yr actuarial FFS = 35%</td>
<td>5-yr actuarial OS = 40%</td>
</tr>
<tr>
<td>Weinstein et al [17]</td>
<td>APO</td>
<td>21</td>
<td>95% CR</td>
<td>3-yr actuarial FFS = 58%</td>
<td>5-yr actuarial OS = 69%</td>
</tr>
<tr>
<td>Hooezer et al [18]</td>
<td>Two ALL-type protocols, both including CNS and</td>
<td>45</td>
<td>93% CR</td>
<td>7-yr actuarial DFS = 62%</td>
<td>7-yr actuarial OS = 51%</td>
</tr>
<tr>
<td>Thomas et al [19]</td>
<td>HyperCVAD</td>
<td>33</td>
<td>91%</td>
<td>3-yr PFS = 66%</td>
<td>3-yr OS = 70%</td>
</tr>
<tr>
<td>Jabbour et al [20]</td>
<td>LMT-89 (ALL-type induction regimen derived)</td>
<td>27</td>
<td>85% OR</td>
<td>5-yr FFP = 44%</td>
<td>5-yr OS = 63%</td>
</tr>
<tr>
<td>Song</td>
<td>“Hybrid” NHL/ALL regimen</td>
<td>34</td>
<td>100% OR</td>
<td>4-yr EFS = 68%</td>
<td>4-yr OS = 72%</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia; APO = doxorubicin (Adriamycin), prednisone, vincristine (Oncovin); CHOP = cyclophosphamide, hydroxydaunomycin, vincristine, prednisone; CNS = central nervous system; CR = complete response; DFS = disease-free survival; EFS = event-free survival; FFP = freedom from progression; FFS = failure-free survival; HyperCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, methotrexate; IPI = International Prognostic Index; NA = not available; NHL = non-Hodgkin lymphoma; OR = overall response; PR = partial response; RFS = relapse-free survival; SCT = stem cell transplantation.
Schema for the hyper-CVAD and modified hyper-CVAD regimens

Deborah A. Thomas et al. Blood 2004;104:1624-1630
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
      - Nellarable/clinical trial/other salvage chemotherapy
      - Allogeneic SCT (MA or RIC)

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

Blood 2015 126:833-841; doi: https://doi.org/10.1182/blood-2014-10-551895
Supportive care

• Allopurinol is recommended for the first 10 days of induction therapy to prevent hyperuricemia.

• Antimicrobial prophylaxis, antiviral and *Pneumocystis jiroveci* pneumonia prophylaxis throughout treatment.

• Fungal prophylaxis should include mold coverage throughout induction therapy.
  – Broader spectrum azole antifungals should be used with caution when using vincristine.

• Asparaginase-related toxicities
  – Asparaginase-related hypersensitivity reactions can occur in 20% of children and adults.
OS from the diagnosis of patients with B- vs T-ALL in the UKALLXII/E2993 trial

Mark R. Litzow, and Adolfo A. Ferrando Blood
2015;126:833-841
Comparison of OS in patients with T-cell ALL who had a matched sibling donor vs those without a donor within the UKALL XII/E2993 trial

David I. Marks, and Clare Rowntree Blood
2017;129:1134-1142
Comparison of OS in patients with T-cell ALL treated with autologous stem cell transplantation (auto) or chemotherapy (chemo) within the UKALL XII/E2993

David I. Marks, and Clare Rowntree Blood
2017;129:1134-1142

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References

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• http://www.slideshare.net/usmlegalaxy/acute-lymphoblastic-lymphoma
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