Chronic Lymphocytic Leukemia (CLL)

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Ayalew Tefferi, M.D.
Mayo Clinic
Rochester, MN, USA

Tefferi.ayalew@mayo.edu

Slides were borrowed from Dr. Timothy Call, CLL expert
Mayo Clinic, Rochester, MN: call.timothy@mayo.edu
Objectives

I. Diagnosis and disease overview
II. Risk stratification
III. Treatment
Diagnosis

- considered in the presence of increased white blood cell count (WBC)
- entertained if the increased WBC is secondary to increased “lymphocytes”
- suspected if the peripheral blood smear reveals that the increased lymphocytes are morphologically “mature” appearing and fragile cells are present
- confirmed by flow cytometry
Differential of blood lymphocytosis

- Reactive
  - Infectious
    - EBV, CMV, HIV, etc.
  - Autoimmune
  - Drug induced
- T-cell leukemia/lymphoma (CD3, CD5)
- NK-cell leukemia/lymphoma (CD16)
- B-cell leukemia/lymphoma (CD19, CD20, surface immunoglobulin light chain restriction)
B- cell leukemia/lymphoma

- **CD5+**
  - **CLL:** CD5+, CD20 (dim), CD23+
  - **Mantle cell lymphoma:** CD5+, CD20+ (bright), CD23-
    FISH: t(11:14) or cyclin D1

- **CD5-**
  - **Marginal zone lymphoma:** CD5-, CD20+ (bright)
  - **Hairy cell leukemia:** CD5-, CD20+ (bright), CD11c/CD22+ (bright), CD103+, TRAP+
  - **Follicular lymphoma:** CD5-, CD20+ (bright), CD10+/
    FISH: t(14:18)

- **CD5+/-**
  - **Lymphoplasmacytic lymphoma** *(Waldenstrom’s macroglobulinemia):*
    CD5 +/-, CD20+
    IgM monoclonal protein (>2.5g/dL)

* Flow cytometric results must be correlated with careful pathologic assessment of morphologic features
Cell surface antigens and antibodies

**Antigens**: CD 5, 20, 19, 23

**Antibodies**: Anti CD 5, 20, 19, 23, etc.

Diagnostic (testing)
B-CLL: Dim CD20 / CD5 & CD23 positive
3 names for the same clonal process

**CLL**
- Chronic lymphocytic leukemia
- ALC >5000/micL

**MBL**
- Monoclonal B-cell lymphocytosis
- ALC <5000/micL

**SLL**
- Small lymphocytic lymphoma
- ALC <5000/micL
  +marrow, nodes, spleen exam/CT

**Chronic lymphocytic leukemia**
- ALC >5000/micL

**Monoclonal B-cell lymphocytosis**
- ALC <5000/micL

**Small lymphocytic lymphoma**
- ALC <5000/micL
  +marrow, nodes, spleen exam/CT
Overview

• Affects ~ 10 people/100,000 in the U.S.

• More frequent in Whites > Blacks > Hispanics > Asians

• Average age at diagnosis is 71 years but ~25% < age 60 and 10% patients < age 50;

• Male to female ~2

• Cause is still unknown? Due to specific exposures
  • Vietnam veterans—Agent Orange--possible
  • Radon?
  • Other?
### Chronic Lymphocytic Leukemia

**5-Year Relative Survival (Percent) by Year of Diagnosis**

<table>
<thead>
<tr>
<th>Year of Diagnosis</th>
<th>All Races</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both Sexes</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>1975-1977(^a)</td>
<td>67.1</td>
<td>64.7</td>
<td>70.3</td>
</tr>
<tr>
<td>1978-1980(^a)</td>
<td>67.8</td>
<td>64.7</td>
<td>71.9</td>
</tr>
<tr>
<td>1981-1983(^a)</td>
<td>65.7</td>
<td>65.0</td>
<td>66.8</td>
</tr>
<tr>
<td>1984-1986(^a)</td>
<td>72.3</td>
<td>71.0</td>
<td>73.9</td>
</tr>
<tr>
<td>1987-1989(^a)</td>
<td>72.7</td>
<td>72.7</td>
<td>72.8</td>
</tr>
<tr>
<td>1990-1992(^a)</td>
<td>74.0</td>
<td>71.7</td>
<td>77.2</td>
</tr>
<tr>
<td>1993-1995(^a)</td>
<td>76.8</td>
<td>76.7</td>
<td>76.9</td>
</tr>
<tr>
<td>1996-1998(^a)</td>
<td>75.2</td>
<td>73.6</td>
<td>77.4</td>
</tr>
<tr>
<td>1999-2003(^a)</td>
<td>79.9</td>
<td>79.4</td>
<td>80.7</td>
</tr>
<tr>
<td>2004-2010(^a)</td>
<td>83.5(^a)</td>
<td>83.1(^a)</td>
<td>84.2(^a)</td>
</tr>
</tbody>
</table>

SEER Cancer Statistics Review 1975-2011
Prognostic factors

• Clinical stage
  
• Fluorescent in situ hybridization (FISH)/cytogenetics

• IGHV (Immunoglobulin heavy chain variable region) mutation analysis (unmutated is bad)

• Beta-2-microglobulin (>2x UNL is bad)

• Others
  • ZAP-70 (Zeta-chain-associated protein kinase 70)
  • CD38 (cluster of differentiation 38)
  • Others
### Risk stratification by clinical parameters

<table>
<thead>
<tr>
<th>Rai Stage</th>
<th>Characteristic</th>
<th>Median Survival</th>
<th>2009*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis only</td>
<td>150</td>
<td>168</td>
</tr>
<tr>
<td>I</td>
<td>Lymphadenopathy</td>
<td>101</td>
<td>120</td>
</tr>
<tr>
<td>II</td>
<td>Organomegaly</td>
<td>71</td>
<td>120</td>
</tr>
<tr>
<td>III</td>
<td>Anemia (Hg&lt;11)</td>
<td>19</td>
<td>60</td>
</tr>
<tr>
<td>IV</td>
<td>Thrombocytopenia (&lt;100)</td>
<td>19</td>
<td>76</td>
</tr>
</tbody>
</table>

*N=2397

*Mayo Clinic CLL Database 2009
Chromosome Anomalies in Chronic Lymphocytic Leukemia

- del(6)(q23)
- +12
- del(11)(q23)
- +12
- del(11)(q23)
- del(17)(p13)
- del(13)(q14)x1
- 6q-
- 17p-
- 11q-
- 13q-
Chromosome Analysis by FISH

17p⁻ 11q⁻ 6q⁻ +12 normal 13q⁻

Dewald et al, Mayo Clinic

<table>
<thead>
<tr>
<th></th>
<th>% OF PATIENTS</th>
<th>MEDIAN SURVIVAL YEARS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>17p⁻</td>
<td>7%</td>
<td>2.5</td>
</tr>
<tr>
<td>11q⁻</td>
<td>17%</td>
<td>6.6</td>
</tr>
<tr>
<td>12+</td>
<td>14%</td>
<td>9</td>
</tr>
<tr>
<td>Normal</td>
<td>18%</td>
<td>9</td>
</tr>
<tr>
<td>13q⁻</td>
<td>36%</td>
<td>11</td>
</tr>
</tbody>
</table>

* Median F/U 70 months
Dohner NEJM 343:1910
The international Prognostic Index for patients with CLL (CLL-IPI): An international meta-analysis.

### CLL International Prognostic Index (CLL-IPI)

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH 17p- or TP53 mutation (4 pts)</td>
<td>4</td>
</tr>
<tr>
<td>IGHV unmutated (2 pts)</td>
<td>2</td>
</tr>
<tr>
<td>β²M &gt;3.5 (2 pts)</td>
<td>2</td>
</tr>
<tr>
<td>Rai stage I-IV / Binet B-C (1 pt)</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;65 (1 pt)</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL POINTS (0-10)</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RISK CATEGORY</th>
<th>POINTS</th>
<th>5-yr TFS % (Mayo)</th>
<th>6-yr OS % (Mayo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal risk</td>
<td>0-1</td>
<td>78%</td>
<td>96%</td>
</tr>
<tr>
<td>Low</td>
<td>2-3</td>
<td>54%</td>
<td>87%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-6</td>
<td>32%</td>
<td>64%</td>
</tr>
<tr>
<td>High</td>
<td>7-10</td>
<td>0%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Kutsch, et. al., J Clin Oncol 33, 2015 (suppl; abstr 7002)
Kutsch, et. al., J Clin Oncol 33, 2015 (suppl; abstr 7002)
Indications to start specific therapy

- “B” symptoms
  - Fever, night sweats, weight loss

- Marrow failure
  - Anemia (Hgb <11)
  - Thrombocytopenia (Platelets <100,000)

- Progressive or symptomatic node/liver/spleen growth

- Autoimmune complications
  - AIHA, ITP, etc.
# Timeline of CLL drug approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>1955</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>1957</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1959</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>1991</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1997—NHL</td>
</tr>
<tr>
<td>Chemoimmunotherapy (FCR/FR/PCR) ~2000-2002</td>
<td></td>
</tr>
<tr>
<td>Bendamustine</td>
<td>2008</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>2009</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>2013</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>2014</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>2014</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>? 2016</td>
</tr>
</tbody>
</table>

*Multiple agents in clinical trials*
B-cell receptor signaling

### Frontline CLL therapy comparisons

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>OR</th>
<th>CR</th>
<th>PFS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA^1 FCR</td>
<td>300</td>
<td>95</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>CLL 10^2 FCR</td>
<td>282</td>
<td>97.8</td>
<td>40.7</td>
<td>53.7</td>
</tr>
<tr>
<td>CLL 10^2 BR</td>
<td>279</td>
<td>97.8</td>
<td>31.5</td>
<td>43.2</td>
</tr>
<tr>
<td>Woyach^3 FR</td>
<td>104</td>
<td>90</td>
<td>47</td>
<td>42</td>
</tr>
<tr>
<td>Kay^4 PCR</td>
<td>64</td>
<td>91</td>
<td>41</td>
<td>32.6</td>
</tr>
<tr>
<td>Goede^5 Obin/ Chlor</td>
<td>333</td>
<td>78</td>
<td>21</td>
<td>26.7</td>
</tr>
<tr>
<td>Goede^5 Ritux/Chlor</td>
<td>330</td>
<td>65</td>
<td>7</td>
<td>15.2</td>
</tr>
<tr>
<td>Resonate 2^6 Ibrutinib</td>
<td>136</td>
<td>86</td>
<td>4</td>
<td>NR@ 18 mo median f/u</td>
</tr>
<tr>
<td>Resonate 2^6 Chlorambucil</td>
<td>133</td>
<td>35</td>
<td>2</td>
<td>18.9</td>
</tr>
</tbody>
</table>

Progression Free Survival

Burger, NEJM 373:2425
Clinical trial: Idelalisib/Rituximab in treatment naïve older patients

- Phase 2 trial of 64 patients ≥ age 65
- Rituximab weekly times 8/Idelalisib oral for minimum of 48 weeks, with option to continue. Median time on Rx 22 months
- Overall response 97%, CR 19%
  - Responses despite 17p- or unmutated
- PFS @ 36 months was 83%
- 67% increased LFT’s w/23% ≥ Grade 3
- 64% diarrhea/colitis

Clinical trial: Not FDA approved frontline

O’Brien, Blood, 126:25, 2686
North American Intergroup Phase 3 CLL Trials

Current Accrual = 447

ECOG 1912

Alliance 041202

CLOSED TO ACCRUAL 12/27/15

Ibrutinib - rituximab

2:1 randomization

Ibrutinib

Bendamustine - rituximab

FCR

age<70
Purine nucleoside analogues (e.g. fludarabine, pentostatin) are discouraged in patients with active autoimmune hemolytic anemia or ITP.
Age > 65-70

CLL: Previously Untreated Meet Criteria for Rx

Fit

Frail or Multiple Comorbidities

Autoimmune cytopenias
  - With significant CLL burden

No 17p-/P53 mutation
  - Clinical Trial
  - Chemoimmunotherapy
    - BR
    - Chlorambucil-obinutuzumab
  - Ibrutinib

17p- or P53 mutation
  - Clinical Trial
  - Ibrutinib
  - Methylpred-rituximab

No 17p-/P53 mutation
  - Ibrutinib
  - Chlorambucil-Obinutuzumab
  - Ofatumumab
  - Methylpred-rituximab
  - Supportive care

Avoid Purine Analogues*
  - Chlorambucil-obinutuzumab
  - Anti CD 20 Moab
  - R-CP
  - R-CD
  - Steroids-rituximab

* Purine nucleoside analogues (e.g. fludarabine, pentostatin) are discouraged in patients with active autoimmune hemolytic anemia or ITP
## Relapsed CLL Therapy Comparison

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ibrutinib&lt;sup&gt;1&lt;/sup&gt; (3y)</th>
<th>Idelalisib&lt;sup&gt;2&lt;/sup&gt; (2y)</th>
<th>Venetoclax&lt;sup&gt;3&lt;/sup&gt; (20m)</th>
<th>BR&lt;sup&gt;4&lt;/sup&gt; (2y)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>BTKi, oral</td>
<td>PI3K&lt;sub&gt;δ&lt;/sub&gt;i, oral</td>
<td>BCL-2i, oral</td>
<td>Chemo, IV</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>90%</td>
<td>72%</td>
<td>80%</td>
<td>59%</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>7%</td>
<td>0%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>MRD-</strong></td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>PFS (median)</strong></td>
<td>&gt; 30m (all), 17p- 25m</td>
<td>16m (all), 17p- 5m</td>
<td>25m (all), 17p- 16m</td>
<td>15m</td>
</tr>
<tr>
<td><strong>Major AE</strong></td>
<td>Pneumonia, HTN, A Fib,</td>
<td>Diarrhea, fever, pneumonia,</td>
<td>Neutropenia (45%), diarrhea,</td>
<td>Neutropenia, thrombocytopenia, anemia, infection</td>
</tr>
<tr>
<td></td>
<td>diarrhea, bleeding,</td>
<td>neutropenia,</td>
<td>infection, TLS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>neutropenia</td>
<td>LFT increase</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RS</strong></td>
<td>7%</td>
<td>? very few</td>
<td>16%</td>
<td>?</td>
</tr>
<tr>
<td><strong>CLL relapse</strong></td>
<td>14%</td>
<td>46%</td>
<td>19%</td>
<td>OS: 34m, &gt;50%</td>
</tr>
</tbody>
</table>

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

- **Idelalisib + Rituximab**
  - **vs**
- **Placebo + Rituximab**
- Overall response
  - **I-R** 81%
  - **Placebo-R** 13%
- **PFS**
  - **I-R** Not reached@ time of publication, ~60% at 14 months
  - **Placebo-R** 5.5 mo.

Furman, NEJM 370:11, 997
CLL: Recurrent/Refractory

Asymptomatic
- Observe or Clinical Trial

Symptomatic
- 17p- or P53 mutation
  - Clinical Trial
  - Ibrutinib
  - Idelalisib
  - Methylpred-anti-CD20
  - Alemtuzumab+/-rituximab
  - If fit, refer transplant eval**
- No 17p-/P53 mutation
  - Fit
    - Clinical Trial
    - Ibrutinib
    - Idelalisib
    - CIT (FCR, PCR, BR)***
    - Methylpred-rituximab
    - Alemtuzumab+/-rituximab
    - Ofatumumab
    - Lenalidomide
    - Consider transplant**
  - Frail
    - Ibrutinib
    - Idelalisib
    - Chlorambucil+/-obinutuz
    - Chlorambucil+/-rituximab
    - Ofatumumab
    - Methylpred-rituximab
    - Supportive care
## Symptoms - Old vs New Treatments

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nausea</td>
<td>1. Infusion reactions-chills, rigors</td>
<td>1. Bruising/bleeding</td>
</tr>
<tr>
<td>2. Vomiting</td>
<td>2. Fever</td>
<td>2. Diarrhea</td>
</tr>
<tr>
<td>5. Low blood counts</td>
<td></td>
<td>5. Muscle/joint aches</td>
</tr>
</tbody>
</table>

6. Heart rhythm changes
# Ibrutinib/ Idelalisib comparisons

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Idelalisib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>1. CLL</td>
<td>1. CLL, relapsed, in which single agent rituximab would be considered</td>
</tr>
<tr>
<td></td>
<td>2. CLL, 17p-, initial Rx</td>
<td>2. SLL, w/ 2 prior Rx</td>
</tr>
<tr>
<td></td>
<td>3. Mantle Cell, w 1 prior Rx</td>
<td>3. Follicular NHL, w/ 2 prior Rx</td>
</tr>
<tr>
<td>Route</td>
<td>oral</td>
<td>oral</td>
</tr>
<tr>
<td>Dose</td>
<td>CLL: 420 mg qd</td>
<td>150 mg bid</td>
</tr>
<tr>
<td></td>
<td>Mantle cell: 560 mg qd</td>
<td></td>
</tr>
<tr>
<td>Single agent use</td>
<td>yes</td>
<td>no-CLL w/ rituximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yes- follicular and SLL</td>
</tr>
<tr>
<td>CYP3A</td>
<td>Moderate inhibitors- decrease dose to 140 mg daily (eg. fluconazole, Cardizem..) Strong inhibitors-avoid (Vori, itra, posi, clarithro..)</td>
<td>Avoid strong CYP3A inhibitors and inducers. It also is itself a strong CYP3A inhibitor. (midazolam)</td>
</tr>
</tbody>
</table>
| Side effects     | Bruising/bleeding, diarrhea, rash, atrial fib, myalgias  
*Hold for 3-7 days before and after surgery* | LFT elevation, diarrhea, colitis, pneumonitis |