Investigation and Management of Chronic Lymphocytic Leukemia

James Johnston
Site Specific Clinics

- **CLL Clinic (787-4454)**
  - Erin Elphee BN
  - James Johnston
  - Rajat Kumar
  - Matt Seftel (transplant)

- **Myeloma Clinic**
  - Vi Dao
  - Ade Olujohungbe

- **Lymphoma Clinics (McCharles, St Boniface and Victoria)**
  - Morel Rubinger
  - James Johnston
  - Ade Olujohungbe
  - Pam Skrabeck
  - Kathy Moltzen

- **Cutaneous Lymphoma**
  - Marni Wiseman
  - James Johnston
## Types of Lymphoproliferative Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B cell lymphoma</td>
<td>24%</td>
</tr>
<tr>
<td>Plasma cell dyscrasias</td>
<td>19%</td>
</tr>
<tr>
<td><strong>CLL/SLL</strong></td>
<td><strong>17%</strong></td>
</tr>
<tr>
<td>Follicular lymphomas</td>
<td>11%</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>10%</td>
</tr>
<tr>
<td>T cell lymphomas, eg, mycosis fungoides</td>
<td>5%</td>
</tr>
<tr>
<td>Lymphoblastic lymphomas/leukemias</td>
<td>5%</td>
</tr>
<tr>
<td>Marginal zone lymphomas</td>
<td>3%</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphomas</td>
<td>2%</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>2%</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>1%</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Blood, 107:265, 2006*
Diagnosis of CLL

- CD19+
- CD5+
- CD23+
### Chronic B Cell Disorders & Flow Cytometry

<table>
<thead>
<tr>
<th></th>
<th>CD19</th>
<th>CD5</th>
<th>CD23</th>
<th>CD10</th>
<th>CD25</th>
<th>CD79b</th>
<th>FMC7</th>
<th>CD103</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Prolymphocytic leukemia</td>
<td>++</td>
<td>-/+</td>
<td>++</td>
<td>-/+</td>
<td>-/+</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-/+</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Follicle centre cell lymphoma</td>
<td>++</td>
<td>-/+</td>
<td>-/+</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Waldenstrom's macroglobulinemia</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
## CLL and Variants

<table>
<thead>
<tr>
<th></th>
<th>CLL</th>
<th>SLL</th>
<th>MBL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B cell count in blood</strong></td>
<td>&gt;5 x 10⁹/L</td>
<td>&lt;5 x 10⁹/L</td>
<td>&lt;5 x 10⁹/L</td>
</tr>
<tr>
<td><strong>Lymphadenopathy/splenomegaly</strong></td>
<td>Maybe</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

**MBL**: Monoclonal B cell lymphocytosis  
**CLL**: Chronic lymphocytic leukemia  
**SLL**: Small lymphocytic lymphoma  

Relevance of MBL?

# Rai Staging for CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Modified Stage</th>
<th>Features</th>
<th>Median Survival (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low-risk</td>
<td>Lymphocytosis</td>
<td>&gt;10</td>
</tr>
<tr>
<td>I</td>
<td>Intermediate-Risk</td>
<td>Lymphadenopathy</td>
<td>7-9</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>Splenomegaly</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>High-Risk</td>
<td>Hgb &lt;110 g/L</td>
<td>2-5</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>Platelets &lt;100 x 10^9/L</td>
<td></td>
</tr>
</tbody>
</table>

- 85% present with Rai stages 0/I disease
- Organomegaly is based on physical exam and not CT scans
Anemia/Thrombocytopenia in CLL

- 24% of patients developed cytopenia at some point in their disease
  - 50% = marrow failure
  - 20% = autoimmune (AID)
  - 30% = “other”, eg, iron deficiency, uremia

- AID: frequency in decreasing order
  - AIHA
  - ITP
  - Red cell aplasia
  - Autoimmune neutropenia

Nowadays, 85% of patients present with stage 0 disease
50% of these will require therapy in 1-4 yrs and have a median survival of 7-8 years
Difficult to predict who will progress
## Predicting Disease Progression

<table>
<thead>
<tr>
<th>Marker</th>
<th>Poorer Prognosis</th>
<th>Better Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;65</td>
<td>&lt;65</td>
</tr>
<tr>
<td>Lymphocyte doubling time</td>
<td>&lt;6 months</td>
<td>&gt;6 months</td>
</tr>
<tr>
<td>Lymphocyte morphology</td>
<td>&gt;30% smudge cells</td>
<td>&lt;30% smudge cells</td>
</tr>
<tr>
<td>β2-microglobulin</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>ZAP-70</td>
<td>≥20% cells +ve</td>
<td>≤19% cells +ve</td>
</tr>
<tr>
<td>CD38</td>
<td>≥20% cells +ve</td>
<td>≤19% cells +ve</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>Del 17, del 11</td>
<td>Del 13 trisomy 12</td>
</tr>
</tbody>
</table>
FISH Abnormalities in CLL

- 55% del 13q
- 18% del 11q*
- 16% trisomy 12q
- 7% del 17p*

54% one abnormality
20% two abnormalities
8% >two abnormalities
82% = total

Dohner et al NEJM, 434:1910, 2000
Other Investigations

- Routine biochemistry
- Immunoglobulin levels
- Serum electrophoresis
- Coomb’s test
Indications for treatment

- Rai stage 0-II disease with progression or significant symptoms
- Rai stages III/IV disease with disease progression
- Uncomfortable organomegaly
- Immune cytopenias
Approaches to Initial Treatment

- Low doses of chlorambucil
- Higher doses of chlorambucil or fludarabine
- Drug combinations, e.g., FC, FR or FCR
- Marrow transplant
Principles of therapy

- Don’t treat based on a lymphocyte count
- Should not receive indefinite treatment with chlorambucil (1 yr maximum)
- Don’t use CHOP unless evidence of transformation to diffuse large B cell lymphoma
- Standard first line treatment is FCR
Untreated, active CLL → FCR → FC → Follow up

**Cycle 1:**
- Fludarabine: 25 mg/m², i.v., d 1-3
- Cyclophosphamide: 250 mg/m², i.v., d 1-3
- Rituximab: 375 mg/m², d 0

**Cycles 2-6:**
- FC + Rituximab
  - Cycle 1: 500 mg/m², d 1

Hallek et al. Lancet, 376:1164, 2010
## Patients of the CLL8 protocol

<table>
<thead>
<tr>
<th></th>
<th>FC (n = 409)</th>
<th>FCR (n = 408)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>105 (26%)</td>
<td>105 (26%)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>304 (74%)</td>
<td>303 (74%)</td>
</tr>
<tr>
<td><strong>Median age</strong></td>
<td>61 (range 36-81)</td>
<td>61 (range 30-80)</td>
</tr>
<tr>
<td><strong>Binet A</strong></td>
<td>22 (5.4%)</td>
<td>18 (4.4%)</td>
</tr>
<tr>
<td><strong>Binet B</strong></td>
<td>259 (63.6%)</td>
<td>263 (64.6%)</td>
</tr>
<tr>
<td><strong>Binet C</strong></td>
<td>126 (31%)</td>
<td>126 (31%)</td>
</tr>
<tr>
<td><strong>B symptoms</strong>*</td>
<td>197 (48%)</td>
<td>167 (41%)</td>
</tr>
<tr>
<td><strong>Median cumulative illness rating scale (CIRS)</strong></td>
<td>1 (range 0-8)</td>
<td>1 (range 0-7)</td>
</tr>
<tr>
<td><strong>Trisomy 12</strong></td>
<td>14.4%</td>
<td>9.6%</td>
</tr>
<tr>
<td><strong>Del(13q)</strong></td>
<td>59.9%</td>
<td>53.7%</td>
</tr>
<tr>
<td><strong>Del(11q23)</strong></td>
<td>22.5%</td>
<td>26.7%</td>
</tr>
<tr>
<td><strong>Del(17p13)</strong></td>
<td>9.5%</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

*P<0.05

Hallek et al. Lancet, 376:1164, 2010
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>FC</th>
<th>FCR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of patients with ≥ 1 grade 3/4 event</strong></td>
<td>248 (62.6%)</td>
<td>309 (77.5%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Hematological toxicity</strong></td>
<td>39.4%</td>
<td>55.7 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>21.0%</td>
<td>33.7%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Leukocytopenia</strong></td>
<td>12.1%</td>
<td>24.0%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>10.9%</td>
<td>7.4%</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>6.8%</td>
<td>5.4%</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>14.9%</td>
<td>18.8%</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Tumor lysis syndrome</strong></td>
<td>0.5%</td>
<td>0.2%</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Cytokine release syndrome</strong></td>
<td>0.0%</td>
<td>0.25</td>
<td>0.32</td>
</tr>
</tbody>
</table>

25% of patients do not complete the 6 cycles of therapy

Hallek et al. Lancet, 376:1164, 2010
# Infectious adverse events

<table>
<thead>
<tr>
<th></th>
<th>FC</th>
<th>FCR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections, total</td>
<td>14.9%</td>
<td>18.8%</td>
<td>0.14</td>
</tr>
<tr>
<td>Infections, if specified</td>
<td>9.3%</td>
<td>13.6%</td>
<td>0.06</td>
</tr>
<tr>
<td>Bacterial</td>
<td>1.3%</td>
<td>2.2%</td>
<td>0.30</td>
</tr>
<tr>
<td>Viral</td>
<td>4.0%</td>
<td>4.2%</td>
<td>0.90</td>
</tr>
<tr>
<td>Fungal</td>
<td>0.3%</td>
<td>0.7%</td>
<td>0.33</td>
</tr>
<tr>
<td>Parasitic</td>
<td>0.0%</td>
<td>0.2%</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Keep patients on prophylactic Septra and Acyclovir

Differences not statistically significant

Treatment related mortality: 2.0% in the FCR and 1.5% in the FC arm

Hallek et al. Lancet, 376:1164, 2010
Progression-Free Survival

Hallek et al. Lancet, 376:1164, 2010
Survival Increased with FCR

Hallek et al. Lancet, 376:1164, 2010
# Prognostic Markers

<table>
<thead>
<tr>
<th></th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Chemoimmunotherapy</td>
<td>0.48 (0.37–0.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum β₂ microglobulin ≥3.5 mg/L</td>
<td>1.40 (1.09–1.81)</td>
<td>0.009</td>
</tr>
<tr>
<td>ECOG performance status ≥1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Serum thymidine kinase ≥10 U/L</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>7.49 (4.83–11.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IGHV unmutated</td>
<td>1.51 (1.11–2.05)</td>
<td>0.008</td>
</tr>
<tr>
<td>White blood cell count ≥50×10⁶ per L</td>
<td>1.41 (1.08–1.86)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Hallek et al. Lancet, 376:1164, 2010
Treatments for CLL in Manitoba

**Fit (CIRS ≤ 6)**
- FCR

**Less fit**
- FR

**Hx of AID**
- CRD

**Fruil**
- Chlorambucil

- High-dose solumedrol
- Campath-1
- Marrow transplant (<65 yrs)

- Ofatumumab
- Lenalidomide

**Resistance**

F, fludarabine; C, cyclophosphamide; R, rituximab; D, dexamethasone

CIRS, Cumulative Illness Rating Scale
## Standard Treatments

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>Number</th>
<th>Previous Treatment</th>
<th>CR (%)</th>
<th>nPR (%)</th>
<th>PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keating et al</td>
<td>FCR</td>
<td>224</td>
<td>No</td>
<td>70</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weirda et al</td>
<td>FCR</td>
<td>177</td>
<td>Yes</td>
<td>25</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallek et al</td>
<td>FCR</td>
<td>388</td>
<td>No</td>
<td>44</td>
<td>-</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>FC</td>
<td>371</td>
<td>No</td>
<td>22</td>
<td>-</td>
<td>67</td>
</tr>
<tr>
<td>Byrd et al</td>
<td>FR</td>
<td>104</td>
<td></td>
<td>38</td>
<td>-</td>
<td>46</td>
</tr>
<tr>
<td>Kay et al</td>
<td>PCR</td>
<td>64</td>
<td></td>
<td>41</td>
<td>22</td>
<td>28</td>
</tr>
</tbody>
</table>
Clinical Trials in CLL Clinic

- Younger patients
  - FCR vs FR vs FR + lenalidomide

- Older patients
  - CLB vs CLB + rituximab vs CLB + RO5072759

- Resistant patients
  - Fludarabine plus valproic acid
Complications of CLL

- Most deaths related to:
  - Progressive CLL, including Richter’s transformation
  - Second malignancies
  - Infections

- Autoimmune problems:
  - 10-20% autoimmune cytopenias
    - AIHA, ITP, autoimmune neutropenia, aplastic anemia
  - Nephrotic syndrome
Treatment of AID

- Initially prednisone 1 mg/kg
  - Septra DS 1 tab po BID at weekends
  - Pamidronate 30 mg iv every 3 months
- If unable to wean off, then add in cyclosporine or cyclophosphamide
- If have active disease or unresponsive to above give CRD
## Risk of AIHA with Chemotherapy

<table>
<thead>
<tr>
<th>739 pts</th>
<th>CLB</th>
<th>FLU</th>
<th>FC</th>
<th>FCR (300 pt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed AIHA</td>
<td>12%</td>
<td>11%</td>
<td>5%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

Case #1

- 2004
  - 52 yr old asymptomatic male
  - No past medical problems
  - Routine assessment
  - WBC 10.0, Lymph 7 x 10^9/L (Normal Hgb & Plts)
  - No lymphadenopathy/splenomegaly
  - Flow cytometry of peripheral blood:
    - T and NK cells, 3 x 10^9/L
    - B cells, 4 x 10^9/L. Cells with CLL immunophenotype
What Rai Stage does he have?

1. Rai 0  
2. Rai I  
3. Rai II  
4. Rai III  
5. Rai IV  
6. None of the above
Many Patients Previously Diagnosed as Rai stage 0 have MBL

- 190 (41%) of 459 pts previously diagnosed as having Rai stage 0 disease now had MBL
- May reduce anxiety and increase ability to get insurance

You would tell patient

1. “Don’t worry, we all have cancer cells in our blood”

2. “You are lucky that we caught your cancer early”

3. “Your disease is unlikely to change and you don’t need any more tests”

4. “Your disease is unlikely to change, but you should still be monitored on a yearly basis”
Patient course

- Patient was referred back in 2009
- Lymphadenopathy
- Fatigue
- CBC
  - Lymphocytes 56 x 10⁹/L
  - Hgb 105 g/L (normal indices)
  - Platelets 90 x 10⁹/L
- What Rai Stage has he?
You would order

1. Hemolytic anemia work-up
2. Ferritin/B12
3. Bone marrow aspirate/biopsy
4. All of the above
Patient course

- Hemolytic anemia work-up
  - Reticulocyte count 20 x 10⁹/L
  - Direct antiglobulin positive
  - LDH, haptoglobin and bilirubin normal
- Ferritin/B12 normal
- Marrow showed 90% CLL cells

Anemia/thrombocytopenia related to marrow packing but patient also has a direct antiglobulin test
Significance of Direct Antiglobulin test

- Occurs in one-third of patients during the course of their disease
- More usually later in the course with more advanced disease
- Can come and go and not necessarily cause hemolysis
- Hemolytic anemia can be triggered by chemotherapy
What do you tell the patient?

- “You’ll be fine. I have lots of patients with CLL who have lived for 30 years”
- “You are more likely to die with this disease than from it”
- “We will see what happens in the next few months”
- “You need to start on treatment as soon as possible”
In 3 months

- **CBC**
  - Lymphocytes $87 \times 10^9/L$
  - Hgb 95 g/L (normal indices)
  - Platelets $75 \times 10^9/L$
What treatment would we use?

1. Chlorambucil
2. Fludarabine
3. FC
4. FR
5. FCR
6. CRD
7. Marrow transplant
Patient course

- Patient treated with FCR
- After 2 cycles of therapy patient returns with increasing fatigue
- Lymphadenopathy resolved
- CBC
  - Hgb 65 g/L (MCV 101fl)
  - Reticulocyte count 250 x 10⁹/L; LDH + bilirubin high and haptoglobin low
  - Lymphocytes 1.1 x 10⁹/L
  - Neutrophils 2.2 x 10⁹/L
  - Platelets 130 x 10⁹/L
- What has he got and what would you do?
Patient Course

1. Treated with prednisone with resolution of his hemolytic anemia
2. Anemia recurred as prednisone reduced
3. Started on CRD chemotherapy and had excellent response
Incidence of immune cytopenias after FCR at MD Anderson

- 300 pts received FCR
- 19 (6.5%) develop immune cytopenias
  - 2 red cell aplasia
  - 17 AIHA (only 20% DAT+ve)
- Median, 4 cycles of FCR
- 5 of 19 after completion of FCR

Borthakur et al. BJH, 136:800, 2007
MD Experience with FCR

- **AIHA**
  - 7/17 responded to steroids alone
  - 6/17 responded to steroids/cyclosporin
  - 4/17 required additional therapy, eg, splenectomy

- **Red cell aplasia**
  - Both responded to cyclosporin

Borthakur et al. BJH, 136:800, 2007
Survival

Borthakur et al. BJH, 136:800, 2007
Patient relapsed 1 year later

What would you do?
Case #2

- 56 yr of man has a routine CBC:
  - Hgb 125 g/L
  - Platelets 155 x 10^9/L
  - WCC 25.4 x 10^9/L
    - Lymphocytes 21 x 10^9/L

- What would you do next?

- Physical examination and flow cytometry
Diagnosed with Rai stage 0 disease. 1 yr later has a Hgb of 90 g/L

What would you do?
Patient turns out to have a colon cancer which is resected

- *Do you think this is related to his CLL?*

Several years later he comes in and tells you his brother has also been diagnosed as having CLL

- *Is there a family connection in the lymphomas and should other family members be screened?*