CLL & SLL: Current Management & Treatment

Dr. Peter Anglin
Chronic Lymphocytic Leukemia

Prolonged clinical course
“Chronic”

A particular type of blood cell – B lymphocyte
“Lymphocytic”

Cancer of white blood cells
“Leukemia” – white blood
Small Lymphocytic Lymphoma

Prolonged clinical course

“Small”

A particular type of blood cell – B lymphocyte

“Lymphocytic”

Cancer of white blood cells

“Lymphoma” – white blood
Same disease. Different location.

CLL & SLL look the same under a microscope.

More cancer cells in the lymphatic system: SLL

More cancer cells in the peripheral blood: CLL

We refer to both as CLL in this presentation unless there is something specific where we have to distinguish between the two.
CLL cells depend on extra-cellular signals that are transmitted by the B cell receptor

Binding to the BCR provides a survival signal “feed me”

Important mediators that transmit BCR signals are:

BTK, the target of ibrutinib
PI3k, the target of Idelalisib
CLL cells depend on BCL2 to survive

Mitochondria “cellular motor”
2 critical roles:
• Provide energy
• Decide cell fate (to live or die)

In CLL, genetic damage triggers P53, the “guardian of the genome”, which in turns stimulates cell death if there is too much damage. BCL2 protects the cell from dying. Cells can also disable P53 to help them survive.

Mitochondrial collapse is an irreversible step to cell death

Causes

• We do not know what causes most cases of CLL.
• There is no way to prevent CLL.
• You can not catch CLL from someone else.
• In some families, more than one blood relative has CLL.
Symptoms

Symptoms from Low White Blood Cells
• Recurrent infections

Symptoms from Low Red Blood Cells
• Shortness of breath and fatigue

Symptoms from Low Platelets
• Bleeding

Other
• Symptoms from consequences of enlarged lymph nodes: may affect internal organs (kidneys- back pain, lungs- cough)
• “B symptoms”: fevers, night sweats and weight loss
• Profound fatigue
Complete blood count (CBC)

<table>
<thead>
<tr>
<th>ANALYTE</th>
<th>RESULT</th>
<th>UNIT</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (Hb)</td>
<td>12.4 g/dl</td>
<td>13.7 - 16.3</td>
<td></td>
</tr>
<tr>
<td>Total RBC</td>
<td>6.4 x10^12/l</td>
<td>4.5 - 6.5</td>
<td></td>
</tr>
<tr>
<td>Hct</td>
<td>41 %</td>
<td>41.9 - 48.7</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>63 fl</td>
<td>75.0 - 95.0</td>
<td></td>
</tr>
<tr>
<td>MCH</td>
<td>19 pg</td>
<td>26.0 - 32.0</td>
<td></td>
</tr>
<tr>
<td>MCHC</td>
<td>30 g/dl</td>
<td>32.0 - 36.0</td>
<td></td>
</tr>
<tr>
<td>Platelet Count</td>
<td>240 x10^9/l</td>
<td>150.0 - 400.0</td>
<td></td>
</tr>
<tr>
<td>WBC Count (TLC)</td>
<td>7.7 x10^9/l</td>
<td>4.0 - 11.0</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>59 %</td>
<td>40.0 - 75.0</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>34 %</td>
<td>20.0 - 45.0</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>3 %</td>
<td>2.0 - 10.0</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>4 %</td>
<td>1.0 - 6.0</td>
<td></td>
</tr>
</tbody>
</table>

Lymphocytosis

No symptoms in 30-40% of people
Peripheral blood smear

- Lymphocytosis
- Low platelets
- Size and shape of red blood cells
- Quantity of other immune cells (neutrophils)
Flow cytometry

- Read the cell’s surface like a barcode
- Detect extremely low levels of CLL in blood or marrow (MBL and MRD)
- CLL: CD19+, CD5+, CD200+, CD23+
Assessment of bone marrow function in some patients
Disease Progression

Majority → Median of 5 years without symptoms followed by progression and complications

30% → Disease free for years and years

15% → Aggressive disease from onset
# Rai staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Median Survival (Months)</th>
<th>Risk Status (Modified Rai)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis, lymphocytes in blood &gt;15,000/mcL and &gt;40% lymphocytes in the bone marrow</td>
<td>140</td>
<td>Low</td>
</tr>
<tr>
<td>I</td>
<td>Stage 0 with enlarged node(s)</td>
<td>100</td>
<td>Intermediate</td>
</tr>
<tr>
<td>II</td>
<td>Stage 0–1 with splenomegaly, hepatomegaly, or both</td>
<td>70</td>
<td>Intermediate</td>
</tr>
<tr>
<td>III</td>
<td>Stage 0–II with hemoglobin &lt;11.0 g/dL or hematocrit &lt;33%</td>
<td>20</td>
<td>High</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 0–III with platelets &lt;100,000/mcL</td>
<td>20</td>
<td>High</td>
</tr>
</tbody>
</table>

Immunoglobulin gene mutation status

Unmutated is more aggressive than mutated

Damle et al
Blood, 1999
Hamblin et al
Cytogenetic status:
chromosome abnormalities are important predictors
of response to chemotherapy

Normal karyotype: 46 chromosomes

Missing one green signal:
“deletion” of a chromosome arm

Fluorescence in situ hybridization
Deletion in chromosome 17p (TP53 gene) is the most important predictor of response

International prognostic index for CLL

3472 treatment-naive CLL patients treated on 13 clinical trials 1950-2010

Risk factors:
17p del(TP53 mut) 4 pts
IGVH mutation 2 pts
B2M > 3.5 2 pts
Rai > 1 to 4 1 pt
Age > 65 yo 1 pt

10 year overall survival
Low risk (0-1) = 79%
Intermediate (2-3) = 39%
High (4-6) = 22%
Very high (7-10) = 4%

International CLL-IPI working group; Lancet Oncology 2016
Richter Transformation: poor outcome

• 1928 Maurice Richter
• Rapid clinical change with the rise of a biologically aggressive sub clone of large lymphoid blasts
  Diffuse Large B Cell Lymphoma
  Hodgkin Lymphoma
  T Cell Lymphomas
• Incidence varies in literature (2-15%)”
• 2-4 years from diagnosis
• Risk poorly understood
Principles of CLL treatment

• Establish treatment goals
• Establish prognostic factors (genetics)
• Decide on
  • standard therapy: based on consensus guidelines from prior phase 3 randomized clinical trials and availability of drugs
  • clinical trials: novel therapies or novel combination therapies not otherwise available as standard of care
Watch and wait

• Synonyms: Watch and Worry; observation, active surveillance or deferred therapy
• Suitable for patients with no symptoms or organ dysfunction
• Rationale:
  • No improvement in overall survival to start therapy before needed
  • Chemotherapy can induce symptoms (side effects) in an asymptomatic patient
  • The best responses to a regimen occur with the first exposure to the drugs (i.e. less effective the second time), therefore usually reserve best treatments when needed.
Indications for treatment

- **Symptoms**
  - Severe fatigue, fevers, night sweats, pain
- **Organ dysfunction**
  - Marrow dysfunction, nodes compressing organs
- **Rapid lymphocyte doubling time < 6 months**
- **Complications of CLL not responding to therapy**
  - Auto-immune hemolytic anemia
Age of diagnosis affects treatment choice
Establish goals of therapy

- Reduced Organ Function
- Life Expectancy unrelated to CLL
- Comorbidities

<table>
<thead>
<tr>
<th>Patients:</th>
<th>Fit</th>
<th>Unfit</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy goal:</td>
<td>Deep remission</td>
<td>Balance of efficacy/toxicity</td>
<td>Do no harm</td>
</tr>
</tbody>
</table>

lymphoma.ca
**CLL: Treatment Options have improved by Decade**

<table>
<thead>
<tr>
<th>Decade</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>5% CR Chemo Alkylator chlorambucil or cyclophosphamide</td>
</tr>
<tr>
<td>1970</td>
<td>5% CR Chemo Purine analogues Fludarabine</td>
</tr>
<tr>
<td>1980</td>
<td>25% CR Chemo combo Purine and alkylators FC</td>
</tr>
<tr>
<td>1990</td>
<td>35% CR Rituximab-chemo FCR</td>
</tr>
<tr>
<td>2000</td>
<td>40% CR Novel targeted &amp; immuno therapies²-⁴</td>
</tr>
<tr>
<td>2017</td>
<td>&gt;70% ORR PFS OS²-⁴</td>
</tr>
</tbody>
</table>

1. Adapted from Kay NE. *Blood*. 2006;107:848.

CR, complete response; PFS, progression-free survival; ORR, overall response rate; OS, overall survival.
Decision regarding treatment: standard of care versus clinical trial

**Standard of care**
- Treatment decision usually based on a prior large trial comparing the old standard to new standard
- Offered in most hospitals
- Less testing/scans

**Clinical trial**
- Access to new options or new drugs
- Can be high risk/high gain
- More rigorous testing
## Differences between chemotherapy and novel agents

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Novel Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Damages/binds DNA, triggering a P53 response, triggers cell death if the damage too extensive</td>
<td>• Trigger cell death via a different mechanism</td>
</tr>
<tr>
<td></td>
<td>• Anti-CD20 antibodies</td>
</tr>
<tr>
<td></td>
<td>• BTK inhibitors</td>
</tr>
<tr>
<td></td>
<td>• PI3Kdelta inhibitors</td>
</tr>
<tr>
<td></td>
<td>• BCL2 inhibitors</td>
</tr>
</tbody>
</table>
# Novel therapies approved by Health Canada*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Class of Agent</th>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine (TREANDA)</td>
<td>Antineoplastic alkylating agent</td>
<td>Previously untreated CLL</td>
</tr>
<tr>
<td>Obinutuzumab (GAZYVA)</td>
<td>Monoclonal type II anti-CD20 antibody</td>
<td>Previously untreated CLL (in combination with chlorambucil)</td>
</tr>
<tr>
<td>Ibrutinib (IMBRUVICA)</td>
<td>Bruton’s Tyrosine Kinase (BTK) inhibitor</td>
<td>Relapsed CLL; previously untreated CLL with 17p deletion or for whom FCR is inappropriate</td>
</tr>
<tr>
<td>Idelalisib (ZYDELIG)</td>
<td>Phosphoinositide 3 kinase-delta (PI3K-δ) inhibitor</td>
<td>Relapsed CLL</td>
</tr>
<tr>
<td>Venetoclax (VENCLEXTA)</td>
<td>BH3 mimetic (BCL2 antagonist)</td>
<td>Relapsed CLL with 17p deletion or for whom there are no other available treatment options</td>
</tr>
</tbody>
</table>
Rituximab
FIT and < 65 years old: FCR fludarabine, cyclophosphamide and rituximab

CLL8 trial
FCR significantly better than FR for progression-free and overall survival

**Definition of FIT** = Physically active, no health problems and normal renal function but only ~25% of CLL patients meet these criteria

**Efficacy of FCR:**
- Complete remission: 45%
- Remission duration: 4-5 years

**Toxicity of FCR:**
- 60-80% get at least one grade 3-4 toxicity
- Short term: neutropenia, infections (25%)
- Treatment related mortality (2-5%)
- 20% don’t finish all 6 courses
- Long term toxicity: 15% (5% MDS/AML)

817 patients

Long term survival with FCR: IGVH mutated status benefits the most with ~60% still in remission after 8 years

Fisher et al. Updated results from the CLL8 trial. Blood 2016
FIT and > 65 years old or UNFIT: bendamustine and rituximab (BR)

Definition of UNFIT:
Age > 70 or younger patients with co-morbidities

CLL10 trial
FCR is better than BR except in > 65 year old where BR is as effective but less toxic than FCR

688 patients


PFS= progression free survival
Obinutuzumab: novel anti-CD20 with increased direct cell death

Obinutuzumab (GA101) Mechanisms of Action

Increased Direct Cell Death
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcγRIIIa

Lower CDC
Type II versus Type I antibody

ADCC = antibody-dependent cell-mediated cytotoxicity
CDC = complement-dependent cytotoxicity

With permission from Goede V et al. Proc ASCO 2013;Abstract 7004.
FIT and > 65 years old or UNFIT: chlorambucil and obinotuzumab

CLL 11 trial: Obinutuzumab + Chlorambucil or Rituximab + Chlorambucil vs Chlorambucil Alone


Clb, confidence interval; Clb, chlorambucil alone; Clb-G, chlorambucil + obinutuzumab; Clb-R, chlorambucil + rituximab.
The Balance Between Efficacy and Safety in Front Line CLL

FR, fludarabine + rituximab; FC, fludarabine + cyclophosphamide; Ob-Clb, obinutuzumab + chlorambucil; R-Clb, rituximab + chlorambucil.

FR, fludarabine + rituximab; FC, fludarabine + cyclophosphamide; Ob-Clb, obinutuzumab + chlorambucil; R-Clb, rituximab + chlorambucil.

Ibrutinib: inhibits BTK downstream of B cell receptor
Ibrutinib

Overall response of 71% but only ~5% achieve a complete response

Ibrutinib inhibits 19 other kinases

Serious side effects:
- Neutropenia
- Cardiac arrhythmias
- Bleeding
Resonate trial

Ibrutinib is superior to Ofatumumab in terms of progression free survival and overall survival in patients with relapsed CLL

Overall response: 40% Ibru vs 4% Ofatumumab. No difference in response based on 17p del status
Ibrutinib

17p del still has a worse outcome compared to other genetic abnormalities

Treatment options for relapsed CLL

• If relapse occurs > 2-3 years, can repeat immuno-chemotherapy

• Targeted therapy (small molecules- taken orally, expensive)
  ➢ BCR inhibitors (ibrutinib and idelalisib)
  ➢ BCL2 Inhibitor (venetoclax) – on trial/compassionate patient access program

• Clinical trial with other novel agents

• Cellular therapies: CAR-T (trial), allogeneic transplant
Idelalisib targets PI3Kδ in CLL (and normal B & T cells)
Idelalisib & Rituximab

At 24 weeks, disease progression occurred in 12 patients (10.9%) with Zydelig + rituximab vs 53 patients (48.2%) with placebo.¹
Venetoclax kills CLL cells that are “primed” to die

Concept by Antony Letai
Venetoclax induces rapid clearance of peripheral blood lymphocytes

# Venetoclax active in 17p del CLL

<table>
<thead>
<tr>
<th>Response</th>
<th>All (n=78)</th>
<th>del(17p) (n=19)</th>
<th>Fludarabine Refractory (n=41)</th>
<th>IGHV Unmutated n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>60 (77)</td>
<td>15 (79)</td>
<td>31 (76)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>18 (23)</td>
<td>5 (26)</td>
<td>9 (22)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>PR, a n (%)</td>
<td>42 (54)</td>
<td>10 (53)</td>
<td>22 (54)</td>
<td>11 (46)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>10 (13)</td>
<td>2 (11)</td>
<td>7 (17)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>2 (3)</td>
<td>1 (5)</td>
<td>1 (3)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>D/C before first (week 6) assessment, n (%)</td>
<td>6 (8)</td>
<td>1 (5)</td>
<td>2 (5)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>
# Allogeneic Transplantation CLL

<table>
<thead>
<tr>
<th>Table 1. Summary of Transplant Characteristics and Survival in the Largest Reported Prospective Studies of RIC HSCT in CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Conditioning regimen</td>
</tr>
<tr>
<td>Donors, % sibling/% MUR</td>
</tr>
<tr>
<td>Median follow-up, months</td>
</tr>
<tr>
<td>Median PFS, %</td>
</tr>
<tr>
<td>Median OS, %</td>
</tr>
</tbody>
</table>

ATG, antithymocyte globulin; Bu, busulfan; CLL, chronic lymphocytic leukemia; Cy, cyclophosphamide; Flu, fludarabine; HSCT, hematopoietic stem cell transplantation; MUR, matched unrelated donor; OS, overall survival; PFS, progression-free survival; R, rituximab; RIC, reduced-intensity conditioning; TBI, total body irradiation; y, years.

Fabienne McClanahan, Clinical Advances in Hematology & Oncology Volume 13, Issue 9 September 2015
Supportive Care

• Promote wellbeing
• Vaccination
  • Annual flu shot
  • Vaccine record
• Majority of patients with CLL will experience serious infection. Keep track of your infections & how long they last.
• Stop smoking, avoid tanning beds, wear sunscreen, check your skin.
Questions?