CLL: disease specific biology and current treatment

Dr. Nathalie Johnson
Disclosures

- Consultant and Advisory boards
  - Roche, Abbvie, Gilead, Jansson, Lundbeck, Merck

- Research funding
  - Roche, Abbvie, Lundbeck
Outline

• CLL 101
  • Biology (unmutated vs mutated and TP53)
• Symptoms
• Diagnosis
• Treatment options
  • First line: chemotherapy vs ibrutinib
  • Relapse (see “future therapy session”)
Chronic Lymphocytic Leukemia

Prolonged clinical course
“Chronic”

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

Cancer of white blood cells
“Leukemia” – white blood
Lymphatic system

- Tonsils
- Thymus Gland
- Lymph Nodes
- Spleen
- Lymph Nodes
- Bone Marrow

LYMPHATIC SYSTEM
Cellular components of immune response

Curtesy of Lara a. Aqrawi, inspired by Abbas

Immune dysfunction in CLL:
1) Decrease normal immune cell numbers
2) Abnormal immune function (auto-immunity)
3) Immune side-effects from chemo and novel therapies
Causes of CLL

- We do not know what causes most cases of CLL.
- There is no way to prevent CLL.
- You cannot catch CLL from someone else.
- In some families, more than one blood relative has CLL.
Difference between CLL and other B cell lymphomas: it highjacks normal B cells at different stages of development.

Bone Marrow

B cell progenitor

Acquire BCR through recombination of IG genes

naive B cell

IG-Unmutated CLL MCL

Clonal expansion SMH

Differentiation (high-affinity BCR)

centroblasts

centrocytes

T

T

FDC

Memory B cell

Plasma cell

Multiple Myeloma

Follicular lymphoma

Apoptosis low-affinity BCR

ANTIGEN

ANTIGEN

ANTIGEN

IG Mutated-CLL

ALL
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
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)**

### Hematology Reports

**SPECIMEN:** 3 cc EDTA BLOOD (Lavender Top)

<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>LOW</td>
<td>13.7 - 16.3</td>
</tr>
<tr>
<td>Total RBC</td>
<td>6.4 x10^12/l</td>
<td>NORMAL</td>
<td>4.5 - 6.5</td>
</tr>
<tr>
<td>Hct</td>
<td>41 %</td>
<td>LOW</td>
<td>41.9 - 48.7</td>
</tr>
<tr>
<td>MCV</td>
<td>63 fl</td>
<td>LOW</td>
<td>75.0 - 95.0</td>
</tr>
<tr>
<td>MCH</td>
<td>19 pg</td>
<td>LOW</td>
<td>26.0 - 32.0</td>
</tr>
<tr>
<td>MCHC</td>
<td>30 g/dl</td>
<td>LOW</td>
<td>32.0 - 36.0</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>240 x10^9/l</td>
<td>LOW</td>
<td>150.0 - 400.0</td>
</tr>
<tr>
<td>WBC Count (TLC)</td>
<td>7.7 x10^9/l</td>
<td>NORMAL</td>
<td>4.0 - 11.0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>59 %</td>
<td>LOW</td>
<td>40.0 - 75.0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>34 %</td>
<td>LOW</td>
<td>20.0 - 45.0</td>
</tr>
<tr>
<td>Monocytes</td>
<td>03 %</td>
<td>LOW</td>
<td>2.0 - 10.0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>04 %</td>
<td>LOW</td>
<td>1.0 - 6.0</td>
</tr>
</tbody>
</table>

**Lymphocytosis**

Impaired production of red blood cells, platelets and neutrophils

**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)

Chronic lymphocytic leukemia

Acute lymphoblastic leukemia
Flow cytometry

• Read the cell’s surface like a barcode
• Detect extremely low levels of CLL in blood or marrow
• 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–I 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 (IGVH) mutation status: Mutated is better than unmutated

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

Normal karyotype: 46 chromosomes

Fluorescence in situ hybridization

Missing one green signal: “deletion” of a chromosome arm
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 unmutated 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%
- Intermed (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
  • When to initiate therapy (observation initially)
  • 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” 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.
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.
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

Patients:
- FIT: Goal DEEP REMISSION
- UNFIT: Balance EFFICACY/TOXICITY
- FRAIL: Do NO HARM
CLL: Treatment Options have improved by Decade

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

CR, complete response; PFS, progression-free survival; ORR, overall response rate; OS, overall survival.

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

Antigen binding site

Cell membrane

CD20 protein

B CELL

Antibody-dependent cellular cytotoxicity mechanism

Macrophage
Natural killer cell
Kupffer cell

FcR

Dead B cell

Complement-dependent cytotoxicity mechanism

Membrane attack complex

Direct apoptosis

CD20 translocation to lipid rafts?

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Nature Reviews | Drug Discovery

lymphoma.ca
FIT and < 65 years old : FCR fludarabine, cyclophosphamide and rituximab

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

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

Efficacy of FCR:
Complete remission: 45%
Remission duration: 4-5 years (average-all)

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)

Long term survival with FCR for IGVH mutated patients: ~60% are still in remission after 8 years

Median remission duration for unmutated < 4 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

Obinutuzumab: novel anti-CD20 with increased direct cell death

Obinutuzumab (GA101) Mechanisms of Action

**Increased Direct Cell Death**
Type II versus Type I antibody

**Lower CDC**
Type II versus Type I antibody

**Enhanced ADCC**
Glycoengineering for increased affinity to FcyRIIIa

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 obinutuzumab

CLL 11 trial: obinutuzumab + chlorambucil or rituximab + chlorambucil vs chlorambucil alone


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

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**Efficacy**

- FCR 4.5 y
- BR 3.5 y
- Ob-Clb ~2.5 y
- R-Clb ~1.5 y

**Toxicity**

- % Grade 3 + adverse events
- FCR 76-91%
- BR 79%
- Ob-Clb 73%
- R-Clb 50-56%

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

Ibrutinib inhibits BTK downstream of the B cell receptor
Resonate 17 trial: Ibrutinib is active in 17p-deleted CLL

- Rationale: median progression free survival for 17p-del is 11 months with FCR chemotherapy
- Resonate 17 enrolled 144 patients with 17p-del. relapsed CLL who received ibrutinib 420 mg daily
- Overall response 83% (64% PR)
- 2 year progression free survival: 63%
- Reasons for stopping ibrutinib:
  - Disease progression: 24%
  - Toxicity: 17%
- Severe infections: 30%
- Major bleeding: 8%

Resonate 2 trial: Ibrutinib improves progression free and overall survival compared to chlorambucil in elderly patients

Excluded 17p del CLL

Burget et al. NEJM 2015
Ibrutinib needs to be taken daily
Overall response of 71% but only ~5% achieve a complete response

Ibrutinib inhibits 19 other kinases and can have serious side effects:
- < 10 % patients in trials
  - Cardiac arrhythmias (10%)
  - Major bleeding (7%)
  -- Hypertension (14%)

Opportunistic infections
Arthralgias
Rash
Edema

Burget et al. NEJM 2015 and Brown et al. JCO 2017
Thus, although the Food and Drug Administration has approved ibrutinib for any line of therapy in any age CLL patient, we urge significant caution in its widespread adoption for frontline therapy, particularly in young, fit patients with a long life expectancy in whom we have no data on frontline ibrutinib and who recently have been suggested to have a higher-risk of relapse.”
Summary of treatment options for patients with untreated CLL in Canada (2017)

• FCR is considered the standard of care for patients who are young, physically fit (25% of patients)

• If ineligible for FCR:
  • BR for all patients $\geq 65$ years and fit
  • Chlorambucil-obinutuzumab for unfit patients or fit $\geq 65$ years
  • Ibrutinib for patients with del 17p or unable to tolerate chemo-immunotherapy
  • Clinical trial