Chronic Lymphocytic Leukemia

Current and future therapeutic options

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CLL – a brief recapitulation

- What is CLL?
- Diagnostic tools
- Prognostic scores
- Treatment of CLL
- Science becomes medicine (novel therapeutic approaches)
The blood smear reveals essential hints leading to the diagnosis.
CLL is a disease of the elderly
→ a minority of patients qualifies for toxic therapy

- Most frequent leukemia in the Western hemisphere.
- Median age at diagnosis: 72 years
- Elderly patients may have comorbidities

<table>
<thead>
<tr>
<th>Age at CLL diagnosis (years)</th>
<th>Patients (%)</th>
<th>Mean comorbidities (all cancer types, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 54</td>
<td>11</td>
<td>n/a</td>
</tr>
<tr>
<td>55–64</td>
<td>19</td>
<td>2.9</td>
</tr>
<tr>
<td>65–74</td>
<td>27</td>
<td>3.6</td>
</tr>
<tr>
<td>75+</td>
<td>43</td>
<td>4.2</td>
</tr>
</tbody>
</table>

The Rai classification allows risk stratification

<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>

* Adapted from the 2008 NCI guidelines; BC Cancer Agency 2008 guidelines.3,4
The Rai classification allows risk stratification.
The Binet classification allows risk stratification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hemoglobin ≥10 g/dL and platelets ≥100,000/mm³ and &lt;3 involved nodal areas</td>
</tr>
<tr>
<td>B</td>
<td>Hemoglobin ≥10 g/dL and platelets ≥100,000/mm³ and ≥3 involved nodal areas</td>
</tr>
<tr>
<td>C</td>
<td>Hemoglobin &lt;10 g/dL and or platelets &lt;100,000/mm³ and any number of involved nodal areas</td>
</tr>
</tbody>
</table>

*Adapted from the 2008 NCI guidelines.³

†Areas of involvement considered for staging are as follows: (1) Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged). (2) Axillae (involvement of both axillae counts as one area). (3) Groins, including superficial femorals (involvement of both groins counts as one area). (4) Palpable spleen. (5) Palpable liver (clinically enlarged).
The Binet classification allows risk stratification.
A novel, molecularly-guided risk score allows more detailed risk stratification

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adverse factor</th>
<th>Hazard ratio for death</th>
<th>Factor - grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal aberration</td>
<td>del(17p)</td>
<td>6.0</td>
<td>6</td>
</tr>
<tr>
<td>s-TK</td>
<td>&gt; 10.0 U/L</td>
<td>2.8</td>
<td>2</td>
</tr>
<tr>
<td>s-β2m</td>
<td>&gt; 3.5 mg/L</td>
<td>2.3</td>
<td>2</td>
</tr>
<tr>
<td>IgHV mutational status</td>
<td>unmutated</td>
<td>1.9</td>
<td>1</td>
</tr>
<tr>
<td>s-β2m</td>
<td>&gt; 1.7 mg/L - ≤ 3.5 mg/L</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>ECOG</td>
<td>&gt; 0</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>del(11q)</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>&gt; 60 years</td>
<td>1.3</td>
<td>1</td>
</tr>
</tbody>
</table>
A novel, molecularly-guided risk score allows more detailed risk stratification.

![Graph showing survival rates for different risk groups.]

- **Low Risk**, 0-2 points (N=300)
  - Survival after 5 years: 95.2%

- **Intermediate risk**, 3-5 points (N=460)
  - Survival after 5 years: 86.9%

- **High risk**, 6-10 points (N=410)
  - Survival after 5 years: 67.7%

- **Very high risk**, > 6 points (N=53)
  - Survival after 5 years: 18.7%

\[ p < 0.0001 \]
Summary I

- CLL is the most common leukemia in the Western World

- CLL is characterized by the accumulation of mature lymphocytes

- Multiple risk scores exist and allow patient stratification

- CLL cells are addicted to micro-environmental stimuli

- Transformation can occur before or after somatic hypermutation
The genetics of high risk CLL
IgVH-unmutated CLL clones are associated with poor prognosis
Two distinct cytogenetic aberrations are associated with poor survival.
Disabling mutations in apoptosis-mediating pathways represent high-risk aberrations in CLL.
CLL is a dynamic disease and clonal evolution represents a clinical challenge
the therapy is often directed at a particular genetic context which may not be shared by all subclones. This relationship between therapy and genetic adaptation is likely to result in convergent evolution, in which a mutation that confers resistance will become highly prevalent in relapsed disease. Indeed, this process has been reported in relapsed T-cell ALL after treatment with nucleoside-analog chemotherapy drugs.

An alternative process contributing to the emergence of continuously more aggressive clones may be entirely independent of differential sensitivity to therapy (Figure 2c). We recently observed a higher number of large subclones (410% of cancer cells) in 149 CLL cases that were exposed to treatment before sampling compared with patients who received therapy after the sample was obtained. This finding of increased clonal diversity with treatment held true even after accounting for potential confounders, such as longer follow-up time. We interpret this observation to result, at least in part, from the outgrowth of many diverse pre-existing minor but fit subclones. This latter interpretation is further supported by our observation of an increased frequency of subclonal-driver events (presumably fitter) in treated relative to untreated patients. Overall, our data support the idea that CLL therapy, by markedly reducing disease bulk, may act as a classic evolutionary restriction point and reset interclonal dynamics. Within this conceptual framework, when subclones with high fitness already exist within a tumor population, treatment could favor the development of more aggressive clones, potentially reducing post-relapse survival. In this context, cytotoxic therapy would effectively remove the incumbent clone—acting like a 'mass extinction' event—and thereby shift the evolutionary landscape in favor of one or more aggressive subclones. Thus, highly fit subclones probably benefit from treatment and exhibit rapid outgrowth. These data provide mechanistic support to the observation that the 'watch and wait' strategy for

Figure 2. Three models of how cancer therapy may accelerate clonal evolution. First, cancer therapy, particularly containing genotoxic agents, can induce novel mutagenesis (a). Second, therapy can accelerate clonal evolution by selecting a clone (here illustrated in red) containing a mutation that confers resistance to the therapeutic agent used (b). The resistance of the selected clone is reflected in the depiction of the cell population after cytoreduction, composed almost entirely of the resistant clone (in red). A third model postulates similar sensitivity to treatment of the different subpopulations, reflected in similar proportions before and after cytoreduction (c). The clearing niche alters the dynamic evolutionary landscape allowing a faster rise of a fitter clone.
Therapeutic interventions shift the selective pressure
Multiple competing clones might exist in the same patient
CLL clones can acquire additional genetic aberrations

**CLL at presentation**
- del13q14 (50%)
- +12 (15%)
- ATM (15%)
- TP53 (5–10%)
- NOTCH1 (10%)
- SF3B1 (5–10%)
- BIRC3 (4%)
- MYD88 (3–5%)

**Chemorefractoriness**
- TP53 (40%)
- BIRC3 (25%)
- SF3B1 (25%)
- ATM (25%)
- NOTCH1 (25%)
- del13q14 (50%)

**RS**
- TP53 (60%)
- NOTCH1 (30%)
- MYC (28%)
- del13q14 (20%)
- +12 (15%)
- ATM (12%)
- SF3B1 (5%)
- BIRC3 (0%)
Summary II

- CLL is the most common leukemia in the Western World
So, how do we actually treat CLL?
Chemotherapy still remains the backbone of CLL therapy

Purine analogue
fludarabine

Alkylating agent
cyclophosphamide
Antibodies constitute an important pillar of CLL therapy.

Rituximab-opsonized B cells are subject to attack and killing by at least three pathways.

1) Complement-mediated membrane attack
2) Phagocytosis by macrophages
3) Antibody-dependent cell-mediated cytotoxicity
CLL8 trial: Overall survival, update 2012
FCR versus FC

Median observation time 5.9 years

FCR 69.4% alive
Median not reached
FC 62.3% alive
Median 86 months

HR 0.68,
95% CI 0.535-0.858
p=0.001

Hallek et al. Lancet 2010; Fischer K et al. ASH 2012
Overall survival after FCR chemoimmunotherapy

Median observation time
5.9 years

Median OS
FCR IGHV mutated
Not reached
FC IGHV mutated
86 months
FC IGHV unmutated
75 months

FC vs. FCR
HR 1.63,
95% CI 0.908 - 2.916

Fischer K et al. iwCLL 2013
When should we initiate treatment?
Study Design

1. Registration
   Binet A stage CLL
   1st Dx ≤ 12 months, GFR 70 ml/min, untreated

2. Central diagnostics
   Assessment of 4 defined risk factors:
   - Unfavorable cytogenetics (del17p, del11q, tri12)
   - Unmutated IGHV status
   - Thymidine kinase > 10 U/L
   - Lymphocyte doubling time ≤ 12 months

3. Risk stratification
   Risk stratification
   High risk
   ≥ 2 risk factors
   - 6 cycles FCR *
   - watch & wait
   Low risk
   < 2 risk factors
   - watch & wait

* FCR dosing: q28d
  Rituximab 375 mg/m² iv, d0, #1,
  Rituximab 500 mg/m² iv, d1, #2-6
  Fludarabine 25 mg/m² iv, d1-3, #1-6
  Cyclophosphamide 250 mg/m² iv, d1-3, #1-6
Study Population

n = 824 patients registered
(FR 401pts, DE 423 pts)

24 patients w/ premature end of study:
PD, withdrawal, false diagnosis, 2nd malignancy

n = 800 patients available for risk stratification

High risk
n = 201 (25.1%)
FCR
n = 100

Low risk
n = 599 (74.9%)
w&w
n = 599
w&w
n = 101

- Primary endpoint: Event-free survival (EFS)
- Assumption: Improvement by FCR from 50 to 70% at month 36
- Median follow up at analysis: 49 months
Primary Endpoint: EFS

Log rank $P < 0.001$

<table>
<thead>
<tr>
<th></th>
<th>N events</th>
<th>Median EFS</th>
<th>5 year EFS</th>
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</thead>
<tbody>
<tr>
<td>HR-FCR</td>
<td>33</td>
<td>n. r.</td>
<td>55.3%</td>
</tr>
<tr>
<td>HR-W&amp;W</td>
<td>78</td>
<td>n. r.</td>
<td>14.8%</td>
</tr>
<tr>
<td>LR-W&amp;W</td>
<td>111</td>
<td>24.2 months</td>
<td>80.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cox regression: Variable</th>
<th>P Value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort assignment</td>
<td>3.815E-43</td>
<td>1.9</td>
<td>1.3 – 2.8</td>
</tr>
<tr>
<td>HR-FCR vs. LR-W&amp;W</td>
<td>0.001</td>
<td>1.9</td>
<td>1.3 – 2.8</td>
</tr>
<tr>
<td>HR-W&amp;W vs. LR-W&amp;W</td>
<td>3.881E-44</td>
<td>8.2</td>
<td>6.1 – 11.0</td>
</tr>
<tr>
<td>HR-FCR vs. HR-W&amp;W</td>
<td>5.846E-12</td>
<td>0.2</td>
<td>0.1 – 0.4</td>
</tr>
</tbody>
</table>
Can we optimize the components of our current regimens?
GA101: Mechanisms of action

Increased Direct Cell Death
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcyRIIIa

Lower CDC
Type II versus Type I antibody

ADCC, antibody-dependent cell-mediated cytotoxicity
CDC, complement-dependent cytotoxicity
CLL11: Study design

(Goede et al. ASH plenary session, Sunday 8 December, abstract #6; New England Journal of Medicine, in press)

Previously untreated CLL with comorbidities
- Total CIRS* score > 6 and/or creatinine clearance < 70 ml/min
- Age ≥ 18 years
- N = 780 (planned)

*Cumulative Illness Rating Scale

Stage I, n = 590

- Chlorambucil x 6 cycles
- GA101 + chlorambucil x 6 cycles
- Rituximab + chlorambucil x 6 cycles

Additional 190 patients to complete stage II

Stage Ia
- G-Clb vs Clb

Stage Ib
- R-Clb vs Clb

Stage II
- G-Clb vs R-Clb

- GA101: 1,000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m² day 1 cycle 1, 500 mg/m² day 1 cycles 2–6, every 28 days
- Clb: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb
Obinutuzumab displays enhanced response rates compared to rituximab, when combined with Clb.
Obinutuzumab displays enhanced response rates compared to rituximab, when combined with Clb.

As measured by central laboratory assessment (ASO-RQ-PCR) at 3 months after end of treatment; bone marrow samples were usually only taken from patients thought to be in CR. MRD, minimal residual disease; BM, bone marrow.
G-Clb enhances OS in CLL patients with comorbidities compared with Clb

Stratified HR: 0.41
95% CI, 0.23-0.74
P=0.0022

Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

Median observation time: G-Clb, 23.2 months; Clb, 20.4 months
No multiplicity adjustment was done for secondary endpoints
Can we be smarter?
CLL results from an imbalance of life and death signals

- BCR
  - BTK, PI3K, Lyn
- TLR
  - MyD88
- NFκB
- Cell Survival

- ATM
- p53
  - NOXA, PUMA
  - Bcl-2
- Programmed Cell Death

Stressors: Chemotherapy, Radiation, Oncogenic stress
CLL results from an imbalance of life and death signals

- BCR
- TLR
- MyD88
- Ibrutinib
- Idelalisib
- NFKB
- Cell Survival

- ATM
- p53
- NOXA, PUMA
- ABT-199
- Programmed Cell Death

Factors:
- Chemotherapy
- Radiation
- Oncogenic stress
Through activating PI3K generates PIP3 to activate AKT signaling.
PTEN is a phosphatase that counteracts PI3K-mediated AKT activation.
PI3K inhibitors have recently been developed
PI3K inhibition proves effective in CLL
BTK inhibitors have recently been developed.
BTK inhibition proves effective in CLL
BCL2 stabilizes the mitochondrial membrane and antagonizes apoptosis.
BCL2 inhibitors have recently been developed.
The BCL2 inhibitor ABT-199 displays remarkable activity against CLL.

Figure 1. Best percent change from baseline in nodal size, as assessed by CT scan*

*CT = computed tomography; del(17p) = deletion of chromosome 17p

*CT assessment occurred at minimum after 6 weeks of treatment in 51 evaluable patients.
Potential future strategies to achieve long-term control of CLL: “sequential triple T”: tailored, targeted, total eradication of MRD

- **Debulking**
  - Mild chemotherapy with agents like bendamustine or fludarabine
  - 1-2 months (1–2 courses)

- **Induction (combination therapy)**
  - Kinase inhibitor(s)
  - Antibody
  - Bcl2 antagonist
  - 6-12 months

- **MRD tailored maintenance (single agents)**
  - Antibody
  - Lenalidomide
  - Kinase inhibitor
  - Bcl2 antagonist
  - 1 year - ∞
Design of a phase II trial for CLL patients (Bendamustine, ABT199, GA101 → BAG trial of the GCLLSG)

- **Debulking**
  - Bendamustine, 0-2 courses

- **Induction**
  - Obinutuzumab + ABT-199 (≈ 6 months)

- **MRD tailored maintenance**
  - Obinutuzumab + ABT-199 until 3 mo. after MRD-

* number of cycles depending on tumor burden

** up to 30 months after completion of last cycle
Summary III

- FC-R chemoimmunotherapy is the standard for fit patients