Risk-Stratified Treatment in Chronic Lymphocytic Leukemia
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Financial Disclosure

The presenters have no financial interests to disclose.
Learning Objectives

1. Assess risk and monitor response to treatment by combining classic leukemia staging methods with novel pathology biomarkers and prognostic factors
2. Discuss strategies for managing side effects of novel therapies, as well as preventing infections
3. Describe best practices for optimizing selection and sequencing of treatments in the upfront and relapsed/refractory settings
4. Explain the role of the advanced practitioner as a member of the collaborative practice team in caring for patients with CLL through the trajectory of their illness
Case Study: Mrs. P

- 7/2008: 71-year-old female with progressive lymphocytosis (dating back to 2005) referred to local hematologist
- Past medical history
  - Diabetes
  - Hypertension and hyperlipidemia
  - Chronic renal insufficiency
  - Primary hyperparathyroidism (secondary to adenoma with intermittent hypercalcemia)
  - Kidney stones
  - Osteoarthritis
  - Gout
  - Vitamin D deficiency
  - Spinal stenosis with related chronic pain
  - Idiopathic pulmonary fibrosis
Case Study: Mrs. P (cont)

- **Subjective**
  - Asymptomatic
  - Intermittent debilitating back pain, followed by a spine specialist and a pain clinic
  - No recent infections

- **Social history**
  - Retired librarian, no chemical/radiation exposure, no military service
  - Married with 2 daughters
  - No smoking or alcohol history

- **Physical exam**
  - No palpable adenopathy
  - No palpable spleen
CLL Diagnosis

- Essential workup for suspected CLL
  - Laboratory evaluation
    - CBC w/differential, peripheral blood smear, comprehensive panel
  - History
    - Performance status
    - B symptoms
  - Physical exam
    - Physical exam, including nodal regions, Waldeyer’s ring and hepato/splenomegaly
  - Definitive pathology
    - Peripheral blood flow cytometry
    - If flow nondiagnostic, consider lymph node biopsy, excisional or incisional preferred
Peripheral blood flow cytometry: 90% of lymphocytes monoclonal, express moderate lambda light chains, and are positive for CD5, CD23 and dim CD20 / negative for CD38, CD10, CD103

Case Study: Mrs. P (cont)

<table>
<thead>
<tr>
<th>Test (Unit)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (K/µL)</td>
<td>36.0</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>72</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.5</td>
</tr>
<tr>
<td>Platelets (K/µL)</td>
<td>173</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.5</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>44</td>
</tr>
</tbody>
</table>
What additional tests are needed for Mrs. P’s diagnosis?

A. None, the diagnosis has been established already
B. Bone marrow biopsy
C. PET scan
Other CLL Workup Considerations

- May be useful
  - Recurrent infections
    - Immunoglobulins
  - Anemia
    - Reticulocyte, haptoglobin, direct Coombs’
    - Bone marrow biopsy
  - Suspected tumor lysis or Richter’s transformation
    - LDH
    - Uric acid
    - PET (only if Richter’s transformation suspected)

- Consider
  - Hep B testing for CD20 monoclonal antibody therapy
  - Pregnancy test/sperm banking/address fertility issues
Which of the following tests are considered valuable or informative in determining prognosis and treatment in a patient with chronic lymphocytic leukemia (CLL)?

A. ZAP-70, JAK2 and BCR-ABL

B. JAK2 and ADMATS13

C. FISH, IgVH mutational status and karyotype

D. None of the above
Case Study: Mrs. P (cont)

- IgVH mutational status: Mutated
- FISH: Normal
- Karyotype: Normal
- No ZAP 70 or B2-microglobulin
- Had recent chest x-ray and abd/pelvis CT for other issues: No lymphadenopathy reported
# CLL Clinical Staging

## Rai Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis (&gt; 5.0K/µL)</td>
</tr>
<tr>
<td>I</td>
<td>Lymphocytosis + lymphadenopathy</td>
</tr>
<tr>
<td>II</td>
<td>Lymphocytosis + hepato/splenomegaly +/- LAD</td>
</tr>
<tr>
<td>III</td>
<td>Lymphocytosis + anemia (Hgb &lt; 11 g/dL) +/- LAD or HSM</td>
</tr>
<tr>
<td>IV</td>
<td>Lymphocytosis + thrombocytopenia (Plt &lt; 100K/µL) +/- LAD or HSM</td>
</tr>
</tbody>
</table>

## Binet Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 3 involved lymphoid sites</td>
</tr>
<tr>
<td>B</td>
<td>≥ 3 involved lymphoid sites</td>
</tr>
<tr>
<td>C</td>
<td>Anemia (Hgb &lt; 10 g/dL) or thrombocytopenia (Plt &lt; 100K/µL)</td>
</tr>
</tbody>
</table>

Rai Stage Survival

IgVH Mutational Status

- DNA sequencing for homology to the most similar germ-line gene
- Unmutated $\geq 98\%$ homology
- $\sim 50\%$ of CLL considered unmutated
- Mut = OS $\sim 25$ years
  - $\sim 80\%$ No therapy
- Unmut = OS $\sim 9$ years
  - $\sim 20\%$ No therapy
- *Exception = Mut VH3-21 similar to unmut
- Constant over time

Karyotype

- Historically, karyotyping was limited because CLL has a very low mitotic rate.
- Now, B-cell mitogens used to stimulate cell division provide more accurate karyotype:
  - CD40-ligand, CpG oligonucleotide, and IL-2
- ~25% to 37% of patients will have additional abnormalities detected by karyotype (after FISH).
- Complex karyotype (>3 abnormalities) repeatedly associated with poor prognosis.
- Can change over time.

FISH used to probe for common/ significant mutations found in CLL

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Associated Gene</th>
<th>Gene Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(13q)</td>
<td>pRb</td>
<td>Tumor suppressor/Tumor survival</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>Multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>Del(11q)</td>
<td>ATM</td>
<td>Cell division/DNA repair</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>P53</td>
<td>Tumor suppressor</td>
</tr>
</tbody>
</table>

Can change over time

http://AtlasGeneticsOncology.org/Anomalies/tri12ID2024.html
Prognosis by FISH

Clonal Evolution

- New techniques
  - Next generation sequencing
  - Whole exome sequencing
- Clonal evolution is affected by treatment
- Much data
- Not quite ready for standard of care

Others

- **CD38**
  - Detected by flow cytometry
  - Cutoff arbitrarily set at $\geq 30\%$ for high risk
  - Even $> 2\%$ correlated with poor prognosis

- **Beta-2-Microglobulin**
  - Correlates with disease stage and tumor burden
  - $> 3$ generally considered poor prognosis

- **ZAP70**
  - Required for normal T-cell signaling
  - Found aberrantly in CLL cells

- Highly variable: Useful for prognosis but not necessarily treatment decisions

Case Study: Mrs. P (cont)

- Asymptomatic
- Rai Stage 0 CLL/Binet A
- Favorable prognostic findings by FISH
Which of the following is an indication to treat CLL?

A. CLL should be treated upon diagnosis in all cases

B. White blood cell count $> 100K/\mu L$

C. Anemia with hemoglobin $< 12 \text{ g/dL}$

D. Symptomatic splenomegaly
Criteria to Treat CLL

- Eligible for clinical trial
- Significant disease-related symptoms
  - Severe fatigue
  - Night sweats
  - Weight loss
  - Fever without infection
- Threatened end-organ dysfunction
- Progressive bulky disease
  - Spleen > 6 cm below costal margin
  - Lymph nodes > 10 cm
- Progressive anemia or thrombocytopenia

NCCN, 2015.
How Cytopenic Is Cytopenic Enough?

- No “One Size Fits All”
- Platelets counts > 100K/µL = minimal clinical risk
- In select patients with stable, mild cytopenias, continued observation may be appropriate
  - Hemoglobin < 11 g/dL
  - Platelets < 100K/µL
- Autoimmune hemolytic anemia (AIHA) or immune thrombocytopenic purpura (ITP) may be treated for cytopenias alone without treating CLL

NCCN, 2015.
Case Study: Mrs. P (cont)

- Early 2008
  - Profound fatigue
  - Other medical problems stable
  - WBC 174K/µL, hemoglobin 10.1 g/dL, platelets 95K/µL
  - FISH repeated: Continues normal
Audience Response Question

Does this patient need therapy?

A. Yes  JL682
B. No   JL683
Previously Untreated CLL Treatment Schema

**Lab-Based Risk**

- FISH = Del(17p)
  - CLL requiring treatment

- FISH = No Del(17p)
  - Not candidate for aggressive therapy (frail/elderly)

**Clinical Risk**

- Candidate for aggressive therapy
- Not candidate for aggressive therapy (frail/elderly)
- Candidate for aggressive therapy
- Not candidate for aggressive therapy (frail/elderly)
Mrs. P: Initial Treatment Options

<table>
<thead>
<tr>
<th>Initial Therapy – No Del(17p) – No Aggressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obinutuzimab +/- chlorambucil</strong></td>
</tr>
<tr>
<td>Ofatumumab + chlorambucil</td>
</tr>
<tr>
<td>Rituximab + chlorambucil</td>
</tr>
<tr>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Pulse steroids</td>
</tr>
<tr>
<td>Rituximab + bendamustine?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Aggressive therapy</strong></td>
</tr>
<tr>
<td>FCR, FR, PCR, BR</td>
</tr>
</tbody>
</table>
Obinutuzumab + Chlorambucil

- 781 pts: Median age 73 yr, CIRS score 8
- Randomized to O + chlorambucil, R + chlorambucil, or chlorambucil
- Primary endpoint: PFS
- Median PFS: 26.7 mo (O+C), 16.3 mo (R+C), 11.1 mo (C)
- O + C = Complete response rate = 22.3%

Chlorambucil and prednisone initiated in March 2008
Counts improve without normalization
Fatigue improves
October 2009: Presents in local ED with lower GI bleed
Colonoscopy shows
- Ischemic colitis
- Diverticulitis
- Positive for C. diff
December 2009
- WBC 80K/µL, hemoglobin 10.8 g/dL, platelets 49K/µL
- Reassess
- New Del(17p) on FISH
- Further treatment needed
Previously Treated CLL Treatment Schema

Lab-Based Risk

CLL requiring treatment

FISH = Del(17p)

Candidate for aggressive therapy

Not candidate for aggressive therapy (frail/elderly)

FISH = No Del(17p)

Candidate for aggressive therapy

Not candidate for aggressive therapy (frail/elderly)

Clinical Risk
Mrs. P: Relapsed/Refractory Options

<table>
<thead>
<tr>
<th>Subsequent Therapy – Del(17p) – No Aggressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ibrutinib</strong></td>
</tr>
<tr>
<td><strong>Idelalisib +/- rituximab</strong></td>
</tr>
<tr>
<td>Lenalidomide +/- rituximab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aggressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose methylprednisolone +/- rituximab</td>
</tr>
<tr>
<td>Alemtuzumab +/- rituximab</td>
</tr>
<tr>
<td>Oxaliplatin, fludarabine, cytarabine, rituximab</td>
</tr>
</tbody>
</table>
Case Study: Mrs. P (cont)

- December 2009: Bendamustine (70 mg/m\(^2\)) and rituximab initiated
- Tolerated very poorly with multiple admissions for nausea, vomiting, dehydration; multiple dose reductions and delays for prolonged neutropenia
- Received 4 cycles
- Post therapy WBC 2K/µL, hemoglobin 12.3 g/dL, Platelets 50K/µL; creatinine 2.0 mL/min
Expected Outcome: BR – Relapsed CLL

- ORR = 59%
  - Del(17p) = 7.1%
- Median follow-up 24 mo
  - EFS = 14.7 mo
  - Del(17p) = 4.8 mo
  - OS = 33.9 mo
  - Del(17p) = 16.3 mo
- Not optimal therapy for del(17p) – especially relapsed

Case Study: Mrs. P (cont)

- 2010–2014
- Notable admission for diarrhea and dehydration due to *C. diff*
  - Asymptomatic a-fib that resolved without intervention after antibiotics, fluid, and electrolyte replacement
- Treated with rituximab 3 times weekly for thrombocytopenia
- Progression within 4–5 months of completing rituximab
- Recurrent infections noted
- Immunoglobulin G < 400
- Monthly IVIG replacement started with improvement of infections
Hypogammaglobulinemia in CLL

- Not well understood
- Disease-related immune defects
- Effects of chemoimmunotherapy
- Incidence ranges from 20% to 70%
- Increased prevalence with length and stage of disease
- Infection is the leading cause of death in patients with CLL

Case Study: Mrs. P (cont)

- February 2014
- WBC 300K/µL, hemoglobin 8.0 g/dL, platelets 86K/µL
- Needs therapy

Subsequent Therapy – Del(17p) – No Aggressive Therapy

- Ibrutinib
- Idelalisib +/- rituximab
- Lenalidomide +/- rituximab
B-Cell Receptor Signaling

http://www.onclive.com/publications/obtn/2013/october-2013/Novel-B-Cell-Receptor-Signaling-Inhibitors-Show-Promise
Expected Outcomes From Ibrutinib

Estimated 30 month OS = 79%

Del(17p) = 65%

Ibrutinib Effects in CLL

- Transient lymphocytosis at initiation = **Not an adverse event!!**
- AEs expected in ≥ 20%
  - Cytopenias
  - Diarrhea
  - Fatigue
  - Musculoskeletal pain
  - Rash
  - Nausea
  - Fever

General Recommendations

- For any ≥ grade 3 adverse event
  - Temporarily discontinue ibrutinib
  - Resume when AE has resolved to ≤ grade 1
  - For 1st occurrence = Resume at same dose
  - For 2nd–3rd occurrence = Reduce by 140 mg (1 tablet)/occurrence
  - For 4th occurrence = Discontinue

- For concurrent use of CYP3A Inhibitors/Inducers
  - Strong inhibitors: Avoid use
    - Anti-retroviral, ketoconazole, posaconazole, voriconazole, clarithromycin
  - Moderate inhibitors: Reduce dose of ibrutinib to 140 mg
    - Fluconazole, ciprofloxacin, erythromycin, calcium channel blockers
  - Strong Inducers: Avoid use
    - Anti-seizure meds

Audience Response Question

Which of the following would exclude this patient from receiving ibrutinib?

A. Absolute requirement for warfarin  JL684
B. History of atrial fibrillation  JL685
C. History of gastrointestinal bleed  JL686
D. Neutrophil count of < 1.0k/uL prior to treatment initiation  JL687

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency</th>
<th>Management</th>
</tr>
</thead>
</table>
| Atrial fibrillation    | 6%–9%     | Manage as usual
|                        |           | Consider need for anticoagulation: Use reversible agent if possible; warfarin not allowed on clinical trials |
After initiation of ibrutinib, Mrs. P needs to have a tooth extracted by her dentist 2 weeks from date of clinic visit. Would you recommend any modification of her ibrutinib therapy?

A. No, she can continue ibrutinib daily  JL688  
B. Yes, she should hold her ibrutinib dose for 3 days prior to and 3 days following the dental extraction  JL689  
C. Yes, she should hold ibrutinib now and resume the day following the surgery  JL690  
D. No, she should not have her tooth extracted  JL691  

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency (%)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>Up to 6 = Severe</td>
<td>Spontaneous: Hold drug, consider risk/benefit Planned surgery: Hold for 3-7 days prior and after surgery</td>
</tr>
</tbody>
</table>
### Other Specific AE Management

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>71%</td>
<td>Monthly CBC</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54%</td>
<td>Temporary discontinuation or growth factors as clinically indicated</td>
</tr>
<tr>
<td>Anemia</td>
<td>44%</td>
<td>Factors as clinically indicated</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63%</td>
<td>Mild/Moderate: Antidiarrheal agents. Severe: Hospitalization, fluids, hold drug</td>
</tr>
<tr>
<td>Infections</td>
<td>Up to 50%</td>
<td>No standard prophylaxis</td>
</tr>
</tbody>
</table>

Long-Term Follow-up: CLL Patients on Ibrutinib

- Median follow-up 20 mo
  - 232 on therapy, 31 PD, and 45 other
  - Richter's transformation (RT): Early ~ 12 mo = 4.5%
    - Median survival following RT was 3.5 mo
  - CLL progression: late ~ 12 mos = 0.3%
    - Median survival following PD was 17.6 mo
  - Mutations in BTK (C481S) or PLCγ2

Idelalisib + Rituximab

- ORR 81% w/ 93% lymph node response
- Median PFS
  - I + R = not reached
  - R = 5.5 mo

## Idelalisib + Rituximab

<table>
<thead>
<tr>
<th>Most Common AEs</th>
<th>Any Grade (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>60</td>
<td>37</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>56</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>25-35</td>
<td>5-8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Chills</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>2</td>
</tr>
</tbody>
</table>

After starting on idelalisib, Mrs. P. develops grade 2 diarrhea with 4-6 liquid stools daily. When she calls your clinic, what should you recommend?

A. Increase fluid intake to 8-10 large glasses of clear liquids daily  JL692
B. Eat frequent small meals (BRAT Diet)  JL693
C. Stop lactose-containing products, high-osmolar supplements, and alcohol  JL694
D. Check stool sample for common infections and if negative, start loperamide  JL695
E. All of the above  JL696

### Audience Response Question

**Adverse Event**

**Diarrhea (14% serious to fatal)**

**Management**

- Severe (>7 stools/day): Hospitalization fluids, steroids, hold drug. Resume at 100 mg bid
- Life-threatening: Discontinue/DO NOT RESUME

### Adverse Event Management

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Plt 25–50K/µL: Monitor weekly</td>
</tr>
<tr>
<td></td>
<td>Plt &lt; 25K/µL: Hold until &gt; 25; resume at 100 mg bid</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>ANC &lt; 1K/µL: Monitor weekly</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 0.5K/µL: Hold until &gt; 0.5; resume at 100 mg bid</td>
</tr>
<tr>
<td>ALT/AST elevations (14% serious to fatal)</td>
<td>5-20× ULN: Hold until &lt;1× ULN; resume at 100 mg bid</td>
</tr>
<tr>
<td></td>
<td>&gt;20× ULN: Discontinue/DO NOT RESUME</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Discontinue/DO NOT RESUME</td>
</tr>
<tr>
<td>Infections</td>
<td>No standard prophylaxis</td>
</tr>
</tbody>
</table>

Case Study: Mrs. P (cont)

- August 2014: Started on ibrutinib
- WBC increased to peak of 500K/µL for 1 month before slow trend downward
- Initial adverse events: Fatigue and multiple soft stools per day
- AEs improved with time
- Currently: WBC 22K/µL, hemoglobin 10 g/dL, platelets 119K/µL
- Now minimal fatigue and 2 soft stools per day
- Plan is to continue until progressive disease or unacceptable toxicity
Role of the Advanced Practitioner in the Care of Patients With CLL

- Newer agents
  - Frequent up-front monitoring visits
  - Education about expected adverse events
  - Management of adverse events

- Oral drug adherence

- Multidisciplinary care

- Patient/family advocacy
  - Financial
  - Psychosocial

- Long-term survival
  - Continuity of care
  - Long-term and late toxicities
Future Directions

- Venetoclax (ABT-199)
  - BCL-2 inhibitor
  - Phase III study
- ACP-196
  - Second-generation BTK inhibitor
  - Phase III study
- CAR-T cell therapy
  - Phase I/II study
- Multiple others…
Key Takeaways

- Diagnosis and prognosis of CLL patients
  - IgVH, FISH, karyotype
- Selection of therapy
  - Performance status
  - FISH
  - Line of therapy
- Novel therapeutic agents
  - Know exclusion criteria and potential adverse events
- Role of advanced practitioner
  - Long-term follow-up
  - Patient education and advocation
Questions?