Optimizing Therapy for Patients with Chronic Lymphocytic Leukemia

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Educational Objectives
At the completion of this activity, the participant will be able to:

- Describe prognostic indicators utilized to individualize therapy decisions for patients with CLL.
- Identify the efficacy and evolving roles of agents in the treatment of CLL.
- Describe toxicities and management recommendations associated with therapies for CLL.

Incidence of CLL
- 60,300 new cases of leukemia in 2018
- Acute leukemias and chronic leukemias
  - CLL accounts for 37% of adult presentations of leukemia
- 20,940 new CLL cases in 2018
  - 12,990 men vs 7950 women
  - 4510 deaths estimated
  - Median age: 67–72 years
  - 5-year survival: 83%
  - CLL often classified as a lymphoma
  - Similar to small lymphocytic lymphoma (SLL)
  - CLL found in blood and bone marrow
  - SLL located in the lymph nodes
  - Etiology
    - No clear occupational or environmental factors
    - Familial association: 1st degree relatives


Clinical Presentation
- Wide range of symptoms including physical and lab findings
- Majority of patients are asymptomatic with CBC showing lymphocytosis on routine blood draw
- Painless, slowly peripheral adenopathy (50%–80%)
  - Most common cervical, supraclavicular, and axillary
  - Wax and wane
- Systemic symptoms (~5%–10% at presentation)
  - Drenching night sweats
  - Weight loss >10% of ideal body weight within previous 6 months
  - Anemia
  - Splenomegaly (25%–55% on presentation)
  - Hepatomegaly (15%–20% on presentation)
  - Skin lesions


Lab Abnormalities
- Lymphocytosis
  - B lymphocytes >5000/mm³
  - Total lymphocytes normal range = 1000–4000/mm³
  - B cell 1%–20%
- Cytopenias
  - Neutropenia, anemia, and thrombocytopenia
  - Autoimmune hemolytic anemia
  - Hypogammaglobulinemia
  - Elevated LDH and beta-2 microglobulin

Staging

<table>
<thead>
<tr>
<th>Risk</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>B</td>
<td>≤2 enlarged LN areas</td>
</tr>
<tr>
<td>Intermediate</td>
<td>I</td>
<td>Lymphocytosis + enlarged lymph nodes (LN)</td>
</tr>
<tr>
<td>High</td>
<td>II</td>
<td>Lymphocytosis + enlarged liver or spleen ± enlarged LN</td>
</tr>
<tr>
<td>All</td>
<td>IV</td>
<td>≤5 enlarged LN areas or anemia (Hgb &lt;10 g/dL) or thrombocytopenia (platelet count &lt;100,000/mm³) ± enlarged liver, spleen, or LN</td>
</tr>
</tbody>
</table>

Modified Rai

<table>
<thead>
<tr>
<th>Binet</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>≤2 enlarged LN areas</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>≥5 enlarged LN areas</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Anemia (Hgb &lt;10 g/dL) or thrombocytopenia (platelet count &lt;100,000/mm³); A or B + lymphocytosis in blood or bone marrow</td>
<td></td>
</tr>
</tbody>
</table>

Incidence of Cytogenetic Abnormalities, n=325

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>No. of Patients (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>13q deletion</td>
<td>178 (55)</td>
</tr>
<tr>
<td>11q deletion</td>
<td>58 (18)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>23 (7)</td>
</tr>
<tr>
<td>12q trisomy</td>
<td>32 (4)</td>
</tr>
<tr>
<td>3q trisomy</td>
<td>9 (3)</td>
</tr>
<tr>
<td>8q trisomy</td>
<td>16 (5)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>21 (6)</td>
</tr>
<tr>
<td>8q trisomy</td>
<td>6 (2)</td>
</tr>
<tr>
<td>t(14q32)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>57 (18)</td>
</tr>
</tbody>
</table>

*175 pts with 1 abnormality; 67 with 2; 26 with ≥ 3.

Cytogenetics and Overall Survival

Prognostic Features

<table>
<thead>
<tr>
<th>Risk</th>
<th>Score</th>
<th>5-Year Overall Survival</th>
<th>10-Year Overall Survival</th>
<th>Treatment Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–1</td>
<td>93%</td>
<td>79%</td>
<td>Do not treat. Watch and wait.</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2–3</td>
<td>79%</td>
<td>39%</td>
<td>Do not treat except if the disease is really symptomatic.</td>
</tr>
<tr>
<td>High</td>
<td>4–6</td>
<td>63%</td>
<td>23%</td>
<td>Treatment indicated except if the disease is asymptomatic.</td>
</tr>
<tr>
<td>Very High</td>
<td>7–10</td>
<td>23%</td>
<td>3.5%</td>
<td>If you need to treat, do not use chemotherapy but rather novel agents or treatment in clinical trials.</td>
</tr>
</tbody>
</table>

CLL International Prognostic Index (IPI)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
<th>5-Year Overall Survival</th>
<th>10-Year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage Rai I–IV or Binet B–C</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2 microglobulin &gt;3.5 mg/L</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGHV mutation status Mutated</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Del(13q) and/or TP53 mutation Present</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>Score</td>
<td>5-Year Overall Survival</td>
<td>10-Year Overall Survival</td>
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<td>3.5%</td>
</tr>
</tbody>
</table>

CLL International Prognostic Index (IPI) and Treatment


Case 1

DK is a 62-year-old woman who presented to her primary care physician for her annual physical examination.

- Physical exam notable for painless enlarged right axillary lymph node
- Performance status: ECOG 0
- Lab findings:
  - WBC: 45,000/mm$^3$ with 79% lymphocytes; hemoglobin: 13 gm/dL; platelets: 140,000/mm$^3$
  - B2 microglobulin 3.6 mg/dl
  - IGHV mutated
- Cytogenetics—negative for del(17p)
- Diagnosis consistent with CLL
- PMH: Hypertension—lisinopril 10 mg daily; menopause—hormone replacement therapy, estradiol/levonorgestrel patch weekly

Indications to Initiate Therapy

- Cytopenias are secondary to bone marrow involvement
- Massive splenomegaly or lymphadenopathy (≥10 cm diameter)
- Progressive lymphocytosis
  - 50% over 2 months, or lymphocyte doubling time <6 months
- Autoimmune anemia and/or thrombocytopenia
  - Not responsive to corticosteroids
- Disease-related symptoms (unintentional weight loss of ≥10% within 6 months, significant fatigue, fevers for ≥2 weeks, or night sweats for >1 month without other evidence of infection)

Selection of First-Line Therapy

- No definitive standard first-line therapy for all patients
- Most first-line therapies have not been compared to one another
- Overall survival (OS) rates are similar
- CR rates, time to progression, and toxicities differ
- Selection based on patient characteristics
  - Tolerance of chemotherapy
  - Comorbidities
  - Older age
  - Del(17p) or TP53 mutation

Treatment Landscape (Prior to Oral Agents)

Chemoimmunotherapy (CIT)

- Purine analogs (eg, fludarabine, pentostatin)
- Alkylating agents (cyclophosphamide, chlorambucil, bendamustine)

Monoclonal Antibodies (immunotherapy)

- Anti-CD20 (rituximab, ofatumumab, obinutuzumab)
- Anti-CD52 (alemtuzumab)

Stem Cell Transplant = only curative option

Anti-CD20 Monoclonal Antibodies (mAbs)

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Type of mAb</th>
<th>Monitoring</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Chimeric</td>
<td>Infusion-related reactions, tumor lysis syndrome (TLS), infections (especially hepatitis B virus, bacterial, fungal), myelosuppression (prolonged), progressive multifocal leukoencephalopathy (PML) (rare), rash with rituximab (can be severe)</td>
<td>Premedication with acetaminophen, diphenhydramine, glucocorticoid, screen for hepatitis B before initiation, avoid live vaccines</td>
</tr>
<tr>
<td>Rituximab and Hyaluronidase (Rituxan Hycela)</td>
<td>Human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab (Gazyva)</td>
<td>Human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofatumumab (Azerra)</td>
<td>Human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Human</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rituximab and Hyaluronidase

- Similar indications as rituximab
- CLL in combination with FCR only
- Subcutaneous, flat dosing
  - 1600 mg/26,800 units (1600 mg rituximab and 26,800 units hyaluronidase human) SC over 7 minutes
- Patients must have received at least 1 full dose of IV rituximab
- Clinically noninferior to rituximab
**Ibrutinib**

- Ibrutinib (Imbruvica) is a first-generation, irreversible Bruton tyrosine kinase (BTK) inhibitor
- Promotes apoptosis, inhibits proliferation, and prevents CLL cells from responding to survival stimuli
- FDA-approved indications
  - CLL with or without del(17p)
  - Monotherapy or in combination with bendamustine and rituximab

**Ibrutinib: Administration**

- For CLL: 420 mg PO daily
- Tablets: 140 mg, 280 mg, 420 mg, and 560 mg
- Capsules: 70 mg
- Note: 140-mg capsules not available as of May 15, 2018
- Take with a full glass of water
- Dose modifications
  - Mild liver impairment
  - Neutropenia
  - Fever
  - Other Grade 3 or 4 toxicities
- Drug interactions
  - Primarily metabolized by cytochrome P450 enzyme 3A (CYP3A)

**RESONATE-2: Ibrutinib versus Chlorambucil in Treatment-Naïve CLL/SLL**

- An international, randomized, phase 3 trial
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, EFS, rate of hematologic improvement, and safety

<table>
<thead>
<tr>
<th>Ibrutinib</th>
<th>420 mg/day until progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil</td>
<td>0.5 mg/kg (up to max of 0.8 mg/kg) on days 1 and 15 of 28-day cycle for up to 12 cycles</td>
</tr>
</tbody>
</table>

**Ibrutinib: Adverse Events**

- Most common (>20%)
  - Thrombocytopenia, neutropenia, and anemia
  - Upper respiratory tract infections
  - Fatigue, pyrexia
  - Diarrhea, nausea
  - Rash
  - Musculoskeletal pain

**Serious Adverse Events**

- Lymphocytosis
  - Peaks within days to weeks, although resolution can take months
  - Resolves when stopping therapy and resumes when restarting therapy
  - Does not represent disease progression
  - Caused by efflux of lymph cells out of lymph nodes into peripheral blood
- Bleeding
  - Grade 3–5 events, 6% (including subdural hematoma, gastrointestinal bleeding, hematoma, post-procedural)
  - Any grade bleeding, <50% (including bruising)
  - May increase risk of hemorrhage in patients receiving anticoagulation or antiplatelet therapies
  - Monitor more closely
- Withhold ibrutinib at least 3–7 days pre/post-surgery


Cardiac Toxicities

- Cardiac arrhythmias (n=1227 patients from randomized controlled trials, ibrutinib vs control arm)
  - Ventricular tachycardia
  - Any grade 1% versus 0.2%; Grade 3 or >: 0.2% versus 0%
  - Atrial arrhythmias (atrial fibrillation and atrial flutter)
  - Any grade 7% versus 1.5%; Grade 3 or >: 2.8% versus 0.3%
- Risk factors: cardiac risk factors, acute infections, prior history
- Periodically monitor for arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea
- Obtain ECG if symptoms develop

Hypertension

- 0%–17%
- Median onset: 4.6 months
- Add or adjust antihypertensives

Infections and Myelosuppression

- Infections (Grades 3–5)
  - 14%–29% of patients
  - Includes bacterial, viral, and fungal infections
  - Cases of Pneumocystis jirovecii pneumonia (PJP) reported
- Myelosuppression (Grade 3–4)
  - Neutropenia: 19%–29%
  - Thrombocytopenia: 5%–13%
  - Anemia: 0%–9%
  - Monitor counts at least monthly

Other Toxicities

- Secondary malignancies
  - 5%–14%
  - Most frequent: nonmelanoma skin cancer, 4%–11%
- Others:
  - Diarrhea (43%)
    - Grade 2, 9%; Grade 3, 3%
    - Median onset: 10 days
    - Self-limited, responds to loperamide
  - Muscle cramping
  - Pneumonitis (rare), discontinue
  - Visual disturbances
    - 10%, all grades
    - Median time to first onset: 85 days
  - BTK inhibitors
  - PI3K inhibitors (idelalisib)
  - BCL-2 inhibitor (venetoclax)

2018 NCCN Guidelines: First-Line Options

<table>
<thead>
<tr>
<th>Preferred Regimens in Patients without del(17p)/TP53 mutation</th>
<th>Frail patients with significant comorbidity</th>
<th>Age ≥65 years, and younger patients with significant comorbidities</th>
<th>Age &lt;65 years, without significant comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil + obinutuzumab*</td>
<td>FCR (fludarabine, cyclophosphamide, rituximab)*</td>
<td>Bortezomib</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Chlorambucil + ofatumumab</td>
<td></td>
<td>Chlorambucil + rituximab</td>
<td></td>
</tr>
</tbody>
</table>

Case 2

Patient KP is a 76 year old woman with CLL and a poor performance status (unfit) needing treatment. She does not have any cytogenetic abnormalities.

Her PMH includes GERD and uncontrolled COPD. She does not want to lose her hair and has difficulty with transportation to and from the infusion center.

What is the best initial choice for treating her CLL?

Relapsed or Refractory Disease

- Differentiate approach based on response to initial therapy
- Relapsed disease: previously achieved a CR or PR, but then progress after ≥6 months
  - These patients may respond to prior therapy or by switching to another therapy within the same class
  - If the initial response is greater than median PFS for a given regimen, re-treat with same regimen
- Refractory disease: fail to achieve a CR or PR with therapy or progress within 6 months of last therapy
  - Will likely not respond to prior therapy
  - Much poorer prognosis

- Select options
  - BTK inhibitors (ibrutinib, acalabrutinib)
  - PI3K inhibitors (idelalisib)
  - BCL-2 inhibitor (venetoclax)

*2018 NCCN Guidelines: First-Line Options
*NCCN Category I recommendation
Choice of Therapy

- No preferred order of regimens to utilize
- Select based on:
  - Current symptoms and disease burden
  - Response to prior regimens
  - Toxocities observed with prior regimens
  - Age
  - Performance status
  - Comorbidities


Idelalisib

- PI3Kδ inhibitor
- Approved for use in relapsed disease with rituximab
- Dose: 150 mg PO twice daily
  - With or without food
- Strengths: 100- and 150-mg tablets

- Dose modifications:
  - Pneumonitis, hepatic dysfunction, diarrhea, myelosuppression, and infections
  - Drug interactions: CYP3A4 substrate


Phase 3 Study 116/117: Rituximab ± Idelalisib in Relapsed CLL

- Primary Endpoint: PFS, OS by subgroup analysis

- Patients with relapsed CLL, not appropriate for cytotoxic therapy; ≥1 prior anti-CD20 or ≥2 prior cytotoxic therapies

- Rituximab* (n=110)
- Patients with relapsed CLL, first dose 375 mg/m², then 500 mg/m² every 2 weeks x4, then every 4 weeks x3

- Primary Study 116
  - Double blind
  - Open label

- Extension Study 117
  - Rituximab 150 mg bid
  - Idelalisib 150 mg bid
  - Open label

- Rituximab 300 mg bid

- Rituximab*

- Placebo bid

PFS with Rituximab ± Idelalisib in Relapsed CLL

- Most patients: ≥65 years old, ≥3 prior hematologic malignancies, ≥3 prior bone marrow function, ≥3 prior cytotoxic therapies

- **Most common toxicities (incidence ≥20%)**
  - Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, and rash
  - Black box warning:
    - Fatal and/or serious hepatotoxicity (11%-18%)
    - Severe diarrhea or colitis (14%-19%)
    - Infections (21%-36%)
    - Pneumonitis (4%)
    - Intestinal perforation
  - Labs: hypertriglyceridemia, hyperglycemia, ↑ALT/AST

- **Liver function tests**
  - Monitor at baseline and every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, then every 1 to 3 months while on therapy
  - Discontinue if LFTs >5X ULN (Grade 3)
  - Continue to monitor weekly until resolved
  - Once resolved, can restart idelalisib at 100 mg twice daily

- **Bilirubin**
  - Monitor at baseline and every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, then every 1 to 3 months while on therapy
  - Discontinue if LFTs >3X ULN (Grade 3)
  - Once resolved, can restart idelalisib at 100 mg twice daily

Idelalisib: Toxicities

- Toxicity Management

**Zydelig [prescribing information]. Foster City, CA: Gilead Sciences, Inc; 2018.**

**Coutré SE, et al. Leuk Lymphoma. 2015;56(10):2779-2786.**
**Toxicity Management**

**Diarrhea/Colitis**
- Monitor routinely as diarrhea can occur at any time
- 2 types:
  1. Self-limiting, onset first 8 weeks, mild-moderate, and responsive to antidiarrheals
  2. Late onset, not responsive to antidiarrheals or antimicrobials, watery, without cramps, consistent with lymphocytic colitis
- Responsive to systemic corticosteroids or budesonide
- Reduce dose or discontinue drug for severe diarrhea
- Median time to resolution ranged between 1 week and 1 month

**Discontinue idelalisib**
- 100 mg
- 8 hours, and 24 hours post
- Time to onset of pneumonitis ranged from 1 to 3 months
- Cough, dyspnea, hypoxia, and interstitial infiltrates on a radiologic exam
- Consider administration of systemic steroids
- **Intestinal Perforation**
- Avoid concomitant administration with drugs such as digoxin and sirolimus
- Reduce dose or discontinue drug for severe diarrhea
- Take with meal and water; do not chew, crush, or break tablets
- 50 mg
- Start at 20 mg and titrate
- CBC should be monitored in all patients at least every 2 weeks for the first 6 months of therapy, and at least weekly for patients with an ANC <1000/mm³
- or
- PJP prophylaxis is warranted in all patients throughout therapy
- Once resolved, can restart idelalisib at 100 mg twice daily

**Pneumonitis**
- Time to onset of pneumonitis ranged from 1 to 3 months
- Cough, dyspnea, hypoxia, and interstitial infiltrates on a radiologic exam
- Consider administration of systemic steroids

**Safety Alert for Idelalisib**
- A drug warning was published on March 21, 2016, regarding an increased serious infection risk in patients receiving idelalisib
- Serious or fatal PIP or cytomegalovirus (CMV) occurred in <1% of patients
- PIP prophylaxis is warranted in all patients throughout therapy
- Patients should be monitored for CMV throughout therapy
- Therapy should be discontinued in patients with evidence of infection or viremia (positive PCR or antigen test)
- CBC should be monitored in all patients at least every 2 weeks for the first 6 months of therapy, and at least weekly for patients with an ANC <1000/mm³
- for first dose of 20 mg and 50 mg
- Predose at subsequent ramp
- Monitor blood counts at least every 2 weeks for the first 6 months of therapy, and at least weekly in patients while neutrophil counts are >1000 cells/mm³
- Discontinue for ANC <200 cells/mm³ or platelets <25,000 cells/mm³
- Once resolved, can restart idelalisib at 100 mg twice daily

**Venetoclax**
- Venetoclax (Venclexa) is a B-cell lymphoma 2 (BCL-2) inhibitor
- Approved for patients with CLL with or without 17p deletion, following at least 1 prior therapy
- May be given with or without rituximab
- Administration:
  - Take with meal and water; do not chew, crush, or break tablets
  - Metabolized by CYP3A4/5
  - P-glycoprotein substrate as well as inhibitor
  - Avoid concomitant administration with drugs such as digoxin and sirolimus

**Assessment and Prophylaxis for TLS**

<table>
<thead>
<tr>
<th>Cancer Burden</th>
<th>Parameters</th>
<th>Hydration</th>
<th>Uric Acid</th>
<th>Monitoring (potassium, uric acid, phosphate, serum creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>All LN &lt;5 cm AND ALC ≥25,000/mm³</td>
<td>Oral 1.5–2 L/day</td>
<td>Allopurinol*</td>
<td>Outpatient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Predose: 4–6 hours, 24 hours post first dose of 20 mg and 50 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Predose at subsequent ramp-up doses</td>
</tr>
<tr>
<td>Medium</td>
<td>Any LN ≥3 cm OR ALC ≥25,000/mm³ AND any LN ≥5 cm</td>
<td>Oral 1.5–2 L/day and consider additional IV hydration</td>
<td>Allopurinol*</td>
<td>Outpatient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Predose: 4–6 hours, 24 hours post first dose of 20 mg and 50 mg</td>
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<td></td>
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<td></td>
<td></td>
<td>Predose at subsequent ramp-up doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider hospitalization for patients with ACS or/and not for first dose of 20 mg and 50 mg</td>
</tr>
<tr>
<td>High</td>
<td>Any LN ≥3 cm OR ALC ≥25,000/mm³ AND any LN ≥5 cm</td>
<td>Oral 1.5–2 L/day AND IV hydration</td>
<td>Allopurinol*, consider redosing if baseline uric acid is elevated</td>
<td>Inpatient for 1st dose of 20 mg and 50 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Predose: 4–6 hours, 24 hours post first dose of 20 mg and 50 mg</td>
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<td></td>
<td></td>
<td>Consider hospitalization for patients with ACS or/and not for first dose of 20 mg and 50 mg</td>
</tr>
</tbody>
</table>

*Start allopurinol 2 days prior to first dose of venetoclax.
MURANO Interim Analysis: Study Design

- Multicenter, randomized, open-label phase III trial

**Study Population**

- Adult pts with Relapsed or Refractory CLL
- Prior bendamustine permitted if DoR ≥ 24 mos (N = 389)

**Venetoclax**

- Monotherapy until PD, unacceptable toxicity, or maximum of 2 yrs from Day 1 of Cycle 1
- Dose ramp-up: 20–400 mg PO daily for 5 wks then 400 mg PO Day 1 of C1–6

**Combination**

- Venetoclax 375 mg/m² on Day 1 of C1, then 500 mg/m² Day 1 of C2–6

**Rituximab**

- 375 mg/m² on Day 1 of C1, then 500 mg/m² Day 1 of C2–6

**Stratification**

- Stratified by del(17p), prior tx response,* geographic region

*High-risk CLL defined as: del(17p); no response to first-line CT-containing tx; or relapsed in ≤ 12 mos after CT or in ≤ 24 mos after chemoimmunotherapy.

**MURANO: Investigator-Assessed PFS (Primary Endpoint)**

![Graph showing PFS (Primary Endpoint)]

**Venetoclax Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%) (N=240)</th>
<th>Grade ≥3 (%) (N=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>45</td>
<td>41</td>
</tr>
<tr>
<td>Anemia</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarhea</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea</td>
<td>33</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

*Most common treatable/unexpected adverse events

**Acalabrutinib**

- Second-generation BTK inhibitor
- Indication: mantle cell lymphoma after at least 1 prior therapy
- Recently added to NCCN CLL Guidelines for relapsed/refractory disease (category 2a)
- Dose: 100 mg PO twice daily
- Available as 100-mg capsules
- Dose modifications: thrombocytopenia, neutropenia

**Phase 1/2 ACE-CL-001 Study, n=134 Patients**

- Multicenter study in patients with relapsed CLL
- Dose escalation phase (phase 1): acalabrutinib 100–400 mg once daily
- Expansion phase (phase 2): acalabrutinib 100 mg twice daily until progressive disease or unacceptable toxicity
- Patients: received a median of 2 (range 1–13) previous therapies for CLL; 23% had chromosome del(17p13.1)
- Median follow-up: 15.8 months (range 0.2–32.4 months)
- ORR, 85%
- PR, 85%
- CR, 2%
- Hematological toxicity, 10%
- Chromosome del(17p13.1), ORR was 100%
- Median follow-up: 19.8 months (range 0.2–32.4 months)
- ORR (CR + PR) 85%
- PR with lymphocytosis, 8%
- Chromosome del(17p13.1), ORR 85%

**Acalabrutinib Toxicities**

- Same adverse event profile and considerations as ibrutinib, but slightly lower reported frequencies
- Most common adverse events: headache, diarrhea, upper respiratory tract infection, infection
- Grade 3/4: neutropenia (11%), pneumonia (10%), hypertension (any grade, 11%; Grade 3/4, 3%), atrial fibrillation (any grade, 3%; Grade 3/4, 2%); no Grade 3 bleeding events
- Headaches commonly observed early and typically resolved over 1–2 months
- Manage with analgesics (acetaminophen and caffeine)

![Graph showing adverse events]

**Calquence [prescribing information]**

Duvelisib

- Duvelisib (Copiktra) PI3K inhibitor with inhibitory activity against PI3K-δ and PI3K-γ isoforms
- Indications
  - Relapsed or refractory CLL or SLL after ≥ 2 prior therapies.
  - Relapsed or refractory follicular lymphoma (FL) after ≥ 2 prior therapies
- Dose: 25 mg PO twice daily with or without food
- Available as 15 mg and 25 mg capsules
- Dose modifications: infections, diarrhea or colitis, cutaneous reactions, pneumonitis, LFT elevations, neutropenia, thrombocytopenia

Duvelisib Toxicties

- Most common adverse reactions (> 20%)
  - Diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia
- Black box warnings and frequency
  - Fatal and/or serious infections 31%
  - Fatal and/or serious diarrhea or colitis 18%
  - Fatal and/or serious cutaneous reactions 5%
  - Fatal and/or serious pneumonitis 5%
- Antibiotic prophylaxis recommended
  - Pneumocystis jirovecii (PJP)
  - Cytomegalovirus (CMV)

Duvelisib Efficacy

- DUO trial: open-label, 2-arm, randomized, phase 3 trial (n=319) of duvelisib 25 mg PO bid versus ofatumumab 300 mg IV x1 dose, then 2000 mg x11 doses
- Median PFS: duvelisib 13.3 months versus ofatumumab 9.9 months (P<0.0001; HR=0.52)
  - Median PFS in patients with del(17p): duvelisib, 12.7 months versus ofatumumab 9 months (P=0.0015; HR=0.43)
- ORR: duvelisib, 73.8% versus ofatumumab, 45.3% (P<0.0001)

2018 NCCN Guidelines: Relapsed/Refractory

<table>
<thead>
<tr>
<th>Preferred Regimens in Patients Without del(17p)/TP53 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with significant comorbidities OR age &gt;65 years, and younger patients with significant comorbidities</td>
</tr>
<tr>
<td>Ibrutinib*</td>
</tr>
<tr>
<td>Venetoclax + rituximab*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preferred Regimens in Patients with del(17p)/TP53 Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
</tr>
<tr>
<td>Venetoclax + rituximab*</td>
</tr>
</tbody>
</table>

Other recommended regimens:
- Acalabrutinib


Role of the Pharmacist

- Evaluation of patients during onboarding process
- Patient and caregiver education
- Continuity of care
- Financial toxicity
- Adherence assessment and strategies
- Complications of CLL and CLL therapies

Case 2

Mrs. KP’s CLL has relapsed after several years on her prior therapy. New information: deletion 17p and BTK C481S mutation. She takes pantoprazole for GERD.

What treatment do you recommend?
**Cost for 1 Month of Oral Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost for 1 Month of Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib 420 mg PO daily</td>
<td>$13,641.49</td>
</tr>
<tr>
<td>Idelalisib 150 mg PO twice daily</td>
<td>$12,259.84</td>
</tr>
<tr>
<td>Venetoclax 400 mg PO daily</td>
<td>$12,486.88</td>
</tr>
<tr>
<td>Acalabrutinib 100 mg PO twice daily</td>
<td>$16,876.80</td>
</tr>
</tbody>
</table>

*Average wholesale price

**Ibrutinib Adherence: RESONATE Subanalysis, n=195, Ibrutinib 420 mg Once Daily**

- Dose intensity (DI) defined as the proportion of actually administered versus planned doses
- Mean 95% (median 100%)
- Median treatment duration of ~9 months
- Overall higher DI associated with longer PFS compared with lower DI
- Regardless of del(17p) and/or TP53 status
- Fewer PFS events occurred in patients with high DI versus those with low DI (12% vs 33%)

**Tailored Adherence Program**

- Consistent baseline assessment that will help tailor follow-up and monitoring plan for patients
- 1–2 weeks following therapy initiation
- Tailor follow-up based on patient responses
- After initial fill
- Routine monitoring at least prior to each refill for symptoms and adherence
- Medication reconciliation
- Flexibility to adjust program based on patient’s responses

**Drug Interactions**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metabolism/ Transport Effects</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acalabrutinib</td>
<td>Substrate: CYP3A4 (major), P- glycoprotein (ABCB1), BCRP/ABCG2</td>
<td>Avoid with strong CYP3A4 inhibitors or inducers, with moderate CYP3A4 inhibitors used short term, with unconjugated testosterone, with modest CYP3A4 inhibitors, reduce acalabrutinib dose to 100 mg PO daily, with strong CYP3A4 inhibitors, reduce acalabrutinib dose to 50 mg PO daily, avoid co-administration with proton pump inhibitors, stagger dosing with H2 receptor antagonists and antacids, with strong CYP3A4 inhibitors used short term, interrupt acalabrutinib temporarily, with moderate CYP3A4 inhibitor, reduce acalabrutinib dose to 100 mg PO daily, with strong CYP3A4 inducer, increase acalabrutinib to 200 mg PO bid, avoid co-administration with proton pump inhibitors, stagger dosing with H2 receptor antagonists and antacids</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>Substrate: CYP3A4 (major)</td>
<td>Avoid with strong and moderate CYP3A4 inhibitors, with strong CYP3A4 inhibitors used short term, avoid strong CYP3A4 inhibitors needed chronically, if a moderate CYP3A4 inhibitor must be used, reduce ibrutinib dose, if taking concurrent strong CYP3A4 inhibitors, monitor closely for ibrutinib toxicity, avoid use of strong CYP3A4 inducers</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>Substrate: CYP3A4 (major), P- glycoprotein (ABCB1), UGT1A1, UGT2B7, BCRP/ABCG2</td>
<td>Avoid with strong CYP3A4 inhibitors or inducers, if taking concomitant strong CYP3A4 inhibitor, monitor closely for signs of idelalisib toxicity</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Substrate: CYP3A4 (major), P- glycoprotein</td>
<td>Avoid concurrent strong CYP3A4 inhibitors or inducers</td>
</tr>
</tbody>
</table>

**Complications of CLL Therapy and Disease**

- Immunodeficiency
- Autoimmune disorders
- Infections
- Myelosuppression (lymphopenia, neutropenia, thrombocytopenia, anemia)
- TLS
- Secondary malignancies
- Richter’s transformation
- Organ-specific (pneumonitis, colitis, diarrhea, atrial fibrillation, hypertension, bleeding, headaches, and others)
Infections

- Most common site: respiratory tract
- Depending on class of drug, risk can be for up to 2 years following completion of therapy
- Treatment-naive patients
  - Bacterial infections with Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa
  - Recurrent bacterial infections with a mucosal origin (respiratory tract, urinary tract)
- Assessment of current and prior regimens for necessary prophylaxis is essential

Infection Risk and Associated Agents Prophylaxis

<table>
<thead>
<tr>
<th>Agents</th>
<th>Risks</th>
<th>Prophylaxis and Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivirals</td>
<td>Viral (HSV, VZV, CMV)</td>
<td>Anti-VP</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Fungal</td>
<td>Nil</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Bacterial</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Prophylaxis is highly controversial. There is not a consensus on prophylactic agents that should be given. Patients with a long history of CLL and multiple therapies are at highest risk of infection.

Future and Pipeline for CLL

- Optimizing combination and sequencing of existing agents
- Creating treatment strategies for patients with high risk of early aggressive disease
- Second-generation PI3K inhibitors: Umbralisib, PIK8 inhibitor
- GS-4059
- BGB-3111
- CC-292
- Entospletinib (GS-9973)
- Selective inhibitor of spleen tyrosine kinase (5k inhibitor)
- Phase 2 trials
- CD19-targeted CAR-T cells

Conclusion

- The landscape of treatment regimens has evolved to oral therapies.
- The CLL pipeline includes new oral agents and combinations of oral oncolytics with chemotherapeutics.
- Despite oral administration, multiple supportive care medications for prevention of complications and ongoing monitoring for optimal adherence is vital.
- Patient support for assessment of financial risk at each therapy decision point is needed.
- Pharmacists have a significant role in care for patients with CLL that spans over multiple years through progressive therapies and complications.

Additional Resources

- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology—Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia, Version 5.2018
- Chronic lymphocytic Leukemia—Leukemia and Lymphoma Society, Issls.org/leukemia/chronic-lymphocytic-leukemia?src=1+20032&sm2
- National Cancer Institute—Chronic Lymphocytic Leukemia Treatment (PDQ): Health Professional Version, cancer.gov/types/leukemia/hp/cll-treatment-pdq
- CLL Society—cllsociety.org
Questions?

Thank You.
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