

## A CONTINUING EDUCATION ACTIVITY



## Risk Assessment and Risk-Adapted Treatment Selection: A Case-Based Approach for Chronic Lymphocytic Leukemia

This activity is supported by an educational grant from Pharmacyclics, LLC, an AbbVie Company, and Janssen Biotech, Inc.

A continuing education article for nurse practitioners, clinical nurse specialists, advanced degree nurses, and oncology and hematology nurses.

**Release date:** July 18, 2017

**Estimated time to complete activity:** 0.5 hour

**Expiration date:** November 13, 2017

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**Journal of the Advanced Practitioner in Oncology**

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### Activity Rationale and Purpose

The therapeutic landscape of chronic lymphocytic leukemia (CLL) continues to change rapidly. Advances in pathology and genomics are also enabling researchers to use genetic tests to make more accurate risk assessments for various subgroups of CLL patients. Translating these advances into improved quality of care at the bedside poses a challenge; meeting this challenge will require continued education for advanced practitioners who are increasingly important members of the oncology care team.

### Intended Audience

The activity's target audience will consist of nurse practitioners, clinical nurse specialists, advanced degree nurses, and oncology and hematology nurses.

## Learning Objectives

After completing this educational activity, participants should be able to:

1. Apply the principles of risk-adapted treatment using case-based scenarios to illustrate the impact of patient attributes and disease specific attributes
2. Manage toxicities associated with newer agents used to treat chronic lymphocytic leukemia
3. Describe the role of oral therapies in treating patients with chronic lymphocytic leukemia

## Continuing Education



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*Selected Patient Cases From the APSHO Regional Lecture Series*

# Risk Assessment and Risk-Adapted Treatment Selection: A Case-Based Approach for Chronic Lymphocytic Leukemia

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From the University of Arizona and Arizona Cancer Center, Tucson, Arizona

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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<https://doi.org/10.6004/jadpro.2017.8.5.6>

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## INTRODUCTION

As the official publication of the Advanced Practitioner Society for Hematology and Oncology (APSHO), JADPRO is pleased to offer Part 3 of an accredited educational activity based on the recently concluded APSHO Regional Lecture Series. Hosted in collaboration with major cancer centers around the country, the APSHO Regional Lecture Series brought case-based didactic presentations and skills workshops to advanced practitioners.

In the spirit of JADPRO, three accredited Grand Rounds articles by Beth Eaby-Sandy, MSN, CRNP, OCN® (non-small cell lung cancer) and Sandra Kurtin, PhDc, ANP-C, AOCN® (multiple myeloma and chronic lymphocytic leukemia)—program chairs for the regional lecture series—offer the same practice-changing information and strategies for advanced practitioners.

In this Grand Rounds article, program chair Sandra Kurtin reviews the prognosis, risk assessment, and treatment for patients with chronic lymphocytic leukemia and assesses four case studies.

You can read Parts 1 and 2 in previous issues of JADPRO or online at [advancedpractitioner.com](http://advancedpractitioner.com). Check out [apsho.org/lectures](http://apsho.org/lectures) for information on registering for upcoming JADPRO Regional Lectures this year at a location near you.

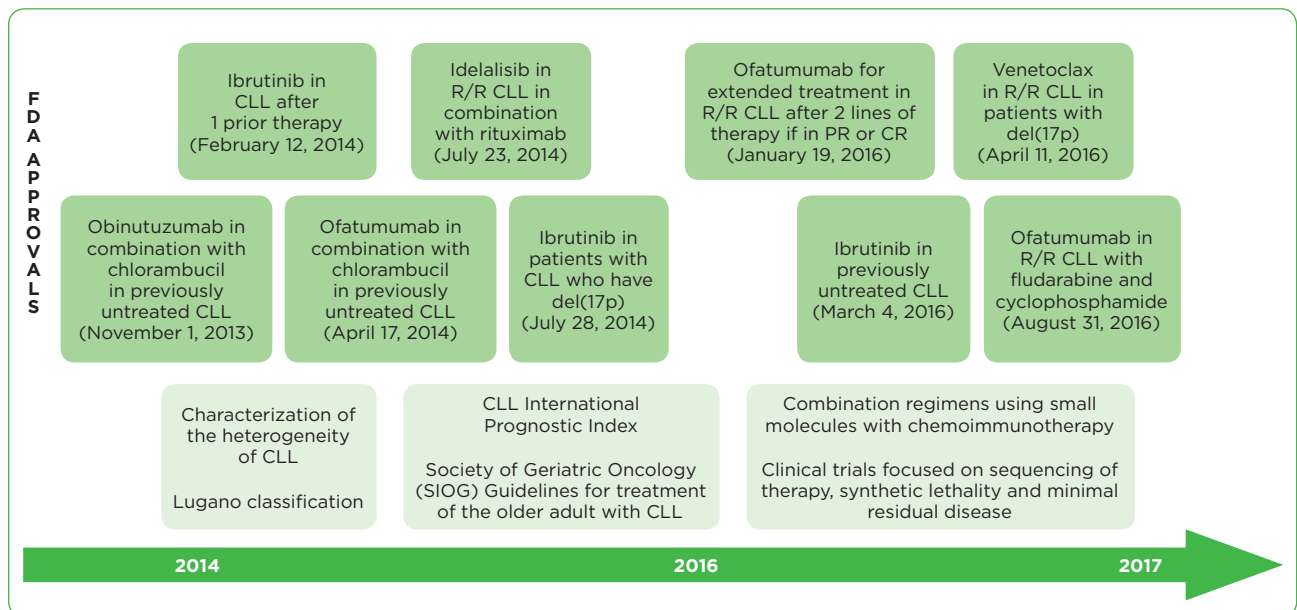
J Adv Pract Oncol 2017;8:502–520

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the United States, with roughly 19,000 new cases diagnosed in 2016 (Siegel, Miller, & Jemal, 2017). The median age at diagnosis is 71 years, with nearly 70% of newly diagnosed patients over the age of 65 (Siegel et al., 2017; Stauder et al., 2016). Chronic lymphocytic leukemia is incurable in the absence of an allogeneic stem cell transplant. The disease trajectory is characterized by periods of stable disease, relapse, and in some cases Richter's transformation. The 5-year relative survival rates have increased from 67.5% (1975–1977) to 81.7% (2005–2011); however, the clinical course of CLL is highly variable, ranging from indolent disease with a median survival exceeding 15 years without treatment, to more aggressive and relatively treatment-resistant disease with median survival of less than 4 years (Eichhorst & Hallek, 2016). This variability in life expectancy is in large part based on the molecular underpinnings of the disease, individual patient characteristics, and access to care.

There have been significant changes in the therapeutic landscape for CLL, due to enhanced

understanding of the molecular features of CLL (Figure 1). In addition, several consensus statements and updated clinical guidelines have been developed. Personalized, tailored therapies based on risk assessment and risk-adapted treatment selection are now the standard of care. Chemoimmunotherapy and small-molecule agents have offered expanded options for treatment, including first-in-class agents. There have been nine US Food and Drug Administration (FDA) approvals for new drugs or expanded applications for existing compounds in less than 3 years. The research pipeline is robust, with additional approvals anticipated in the next 1 to 2 years. These advances offer hope to patients with CLL but require careful application of both diagnostic and prognostic strategies to achieve the improved clinical outcomes demonstrated in clinical trials.

The implications for oncology providers, including the advanced practitioner, are multifaceted. Lifelong learning, involvement in scientific discovery, vigilance in observing and reporting clinical experiences with novel agents in the postmarketing setting, familiarity with metrics for value-based care, and a commitment to improving patient outcomes will be necessary. The purpose of this article



**Figure 1.** Scientific and therapeutic innovation in chronic lymphocytic leukemia 2013–2017.

R/R = relapsed/refractory; PR = partial response; CR = complete response. Information from Balducci & Dolan (2015); Parikh & Shanafelt (2016); Pflug et al. (2014); Rai & Jain (2016); Wierda (2015); Wierda et al. (2017).

is to provide the advanced practitioner in oncology with an update on risk assessment and risk-adapted treatment selection in patients with CLL using a case-based approach to demonstrate application of emerging data. The focus will be on the management of patients with currently approved agents, with mention of emerging therapies.

## PREDICTIVE AND PROGNOSTIC FEATURES OF CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia is characterized by mature B lymphocytes with an immunophenotype including CD5+, CD19+, CD20 weak, CD23+, and weak-surface expression of monoclonal immunoglobulin (SmIg-weak; Gruber & Wu, 2014). Small lymphocytic lymphoma (SLL) has the same immunophenotype as CLL but includes a predominance of nodal disease, bone marrow involvement, organomegaly, and < 5,000 tumor cells/ $\mu$ L. The clinical characteristics of the disease provided the basis for staging and prognosis for the past 50 years.

More recently, advances in flow cytometry, fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS) have elucidated features of the disease that confer either a favorable or unfavorable clinical course—and in some cases implications for treatment (Table 1). Features considered to confer an inferior survival advantage and in some cases refractory disease include the deletion of 17p or mutation of *TP53*, the presence of 11q or a complex karyotype (> 3 abnormalities in > 1 cell), < 2% (unmutated) immunoglobulin heavy-chain gene variable region (IgHV) mutation (uIgHV), > 30% CD38, and > 20% zeta-chain-associated protein 70 (ZAP-70; Parikh & Shanafelt, 2016).

Patients with uIgHV tend to have more aggressive disease, high expression of CD38, ZAP-70–positive disease, poor risk genetic profiles, and shorter survival (Montserrat et al., 2016). In a recent systematic review and meta-analysis including 31 studies, uIgHV was associated with inferior median progression-free survival (PFS; range, 1–5 years) and median overall survival (OS; range, 3.2–10 years) compared with patients with mutated IgHV (median PFS range, 9.2–18.9 years; median OS range, 17.9–25.8 years; Parikh, Strati,

Tsang, West, & Shanafelt, 2016). In this same analysis, patients with del(17p13) and del(11q23), considered FISH high risk, had significantly shorter median PFS (range, 0.1–5.2 years) and median OS (range, 3.3–9.7 years) compared with patients with FISH low/intermediate-risk profiles including del(13q), normal, and trisomy 12 (median PFS range, 1.5–22 years; median OS range, 7.5–20.5 years; Parikh et al., 2016). Chronic lymphocytic leukemia with high expression of CD38 confers a less favorable prognosis due to the association of CD38 with migration and homing of CLL cells to secondary lymphoid organs. The malignant cells receive support from the tumor microenvironment in these lymphoid organs, causing suppression of immune surveillance through the production of tolerogenic compounds and increasing the risk of Richter's transformation (Burgler, 2015; Parikh & Shanafelt, 2014). The tyrosine kinase ZAP-70, involved in cellular signaling of T cells, has been shown to correlate with the presence of uIgHV.

The heterogeneity of CLL is compounded by clonal evolution characterized by acquired genetic and epigenetic changes, which give rise to new subclones with emergence of one or more fitter or resistant subclones that become dominant (Guieze & Wu, 2015). Therefore, full characterization of the disease at the time of initial diagnosis and at disease progression is critical to effective risk analysis, prognostication, and clinical management of CLL. This includes reimaging; excisional biopsies in the case of rapidly progressive adenopathy; and a bone marrow biopsy with flow cytometry, FISH, and NGS when available to obtain a full molecular profile (Eichhorst & Hallek, 2016). Reevaluation of comorbidities and fitness for treatment is necessary for the optimal selection of treatment.

## RISK ASSESSMENT AND PROGNOSTICATION

Given the heterogeneity of the disease, an international consortium of CLL experts convened to develop an internationally applicable prognostic index for CLL: the CLL-International Prognostic Index (CLL-IPI; 2016). Based on a retrospective analysis of 26 different items, 5 items were found to be independent predictors for OS (age, clinical

**Table 1. Biomarkers and Clinical Attributes Used for Risk Assessment in Chronic Lymphocytic Leukemia**

Attribute	Clinical significance	Median OS (yr)
17p13 deletion	<ul style="list-style-type: none"> <li>Present in 5%–20% of cases at the time of first-line treatment, 20%–40% in relapsed/refractory disease</li> <li>Associated with <i>TP53</i> mutation</li> <li>Unfavorable, inferior survival, resistance to chemoimmunotherapy</li> <li>Predisposed to aggressive tempo, Richter's transformation, clonal evolution, and complex karyotype</li> </ul>	4
11q22-23 deletion	<ul style="list-style-type: none"> <li>Present in 20%–25% of cases</li> <li>Intermediate risk</li> <li>Associated with <i>SF3B1</i>, <i>ATM</i>, and <i>BIRC</i> mutations</li> </ul>	6
13q14 deletion	<ul style="list-style-type: none"> <li>Present in 25%–40% of cases</li> <li>Favorable risk when a sole abnormality, associated with <i>MYD88</i> mutations</li> </ul>	15
Trisomy 12	<ul style="list-style-type: none"> <li>Present in 15%–20% of cases</li> <li>Intermediate risk</li> <li>Associated with <i>NOTCH1</i> mutations, atypical immunophenotype</li> <li>Limited to no benefit from anti-CD20 antibodies</li> </ul>	7.5
Complex karyotype	<ul style="list-style-type: none"> <li>Unfavorable</li> <li>Inferior survival</li> <li>Associated with <i>del(17p)/TP53</i> mutation, advanced stage, CD38 expression, and elevated <math>\beta_2</math> microglobulin</li> </ul>	–
<i>TP53</i> mutation	<ul style="list-style-type: none"> <li>Unfavorable</li> <li>Inferior survival, resistance to chemoimmunotherapy</li> <li>Requires gene sequencing</li> </ul>	–
<i>SF3B1</i> mutation	<ul style="list-style-type: none"> <li>Unfavorable</li> <li>Correlates to Richter's transformation</li> <li>Associated with <i>del(11q)</i></li> <li>Inferior response to chemoimmunotherapy</li> <li>Requires gene sequencing</li> </ul>	–
<i>NOTCH1</i> mutation	<ul style="list-style-type: none"> <li>Unfavorable</li> <li>Correlates to Richter's transformation</li> <li>Limited response to anti-CD20 antibodies</li> <li>Requires gene sequencing</li> </ul>	–
< 2% IgHV mutation (ulgHV)	<ul style="list-style-type: none"> <li>Present in 40% of cases</li> <li>Unfavorable</li> <li>Correlated with <i>TP53</i>, <i>NOTCH1</i>, <i>SF3B1</i>, <i>POT1</i> and <i>XPO1</i> mutations, high expression of CD38, ZAP-70, and CD49d</li> <li>Correlated with aggressive tempo, shorter time to first treatment</li> </ul>	3–6
> 2% IgHV mutation (mlgHV)	<ul style="list-style-type: none"> <li>Present in 60% of cases</li> <li>Favorable</li> <li>Correlates with indolent disease, lack of unfavorable genetic features, longer time to first treatment</li> <li>Response to chemoimmunotherapy may translate to sustained MRD status, and OS like in normal healthy subjects</li> </ul>	> 15
> 30% CD38	<ul style="list-style-type: none"> <li>CD38 confers a less favorable prognosis due to the association of CD38 with migration and homing of CLL cells to secondary lymphoid organs</li> </ul>	–
> 20% ZAP-70	<ul style="list-style-type: none"> <li>Unfavorable</li> <li>Higher expression in ulgHV—used as a surrogate measure of ulgHV</li> </ul>	–
$\beta_2$ microglobulin > 3.5 mg/L	<ul style="list-style-type: none"> <li>Unfavorable</li> <li>Shorter time to initial treatment, lower complete remission rates, and shorter overall survival when receiving initial therapy with fludarabine-based regimens</li> </ul>	–
CIRS > 6	<ul style="list-style-type: none"> <li>Correlates with age &gt; 65, CrCl &lt; 70 mL/min, ECOG <math>\geq</math> 2, and <math>\beta_2</math> microglobulin &gt; 3.5 mg/L</li> <li>Fludarabine-based regimens do not add survival advantage when used as first-line treatment</li> <li>Score is based on the number of organ systems involved and the level of control for each comorbidity</li> </ul>	–
Age > 65	<ul style="list-style-type: none"> <li>Correlates with increased CIRS</li> </ul>	–
Rai stage	<ul style="list-style-type: none"> <li>Stage 0 (low risk): Lymphocytosis in blood and marrow only</li> <li>Stage I and II (intermediate risk): Lymphadenopathy, splenomegaly <math>\pm</math> hepatomegaly</li> <li>Stage III and IV (high risk): Anemia (Hgb &lt; 11.0 g/dL); thrombocytopenia (Plt &lt; 100 <math>\times</math> 10<sup>9</sup>/L) + lymphadenopathy and splenomegaly</li> </ul>	12.5 5.9–8.4 1.5

Note. OS = overall survival; ZAP-70 = zeta-chain-associated protein 70; MRD = minimal residual disease; CLL = chronic lymphocytic leukemia; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; CIRS = Cumulative Illness Rating Score; Hgb = hemoglobin; Plt = platelets. Information from Eichhorst & Hallek (2016); Miller et al. (1992); Parikh & Shanafelt (2016); Rai et al. (1975); Roos-Weil, Nguyen-Khac, & Bernard (2016); Rossi, Gerber, & Stussi (2017).

stage, 17p del and/or *TP53* mutation, IgHV status, and  $\beta_2$  microglobulin). Each item was weighted according to regression analysis, with the presence of del(17p) or *TP53* mutation carrying the highest weight (score of 4; hazard ratio [HR]: 4.2;  $p < .001$ ). When combined, these five factors produced four groups with significantly different OS rates (93%, 79%, 64%, and 23% at 5 years;  $p < .001$ ; the International CLL-IPI Working Group, 2016; Table 2).

Given the older age of most patients with CLL, consideration of fitness and frailty as well as the presence of comorbidities is crucial when considering treatment (Goede et al., 2014; Stauder et al., 2016). The presence of comorbidities, particularly when poorly controlled, is associated with an increased risk of treatment-related adverse events, inferior survival, decreased access to care, and inferior quality of life (Sarfati et al., 2016).

### RISK-ADAPTED TREATMENT SELECTION

The goals of therapy in CLL include early identification of high-risk disease, estimation of the time to treatment, early identification of lack of or loss of response to treatment, prevention of infections, preservation of future treatment options by limiting end-organ damage and cumu-

lative treatment toxicity, and ultimately maintenance or improvement in quality of life. Applying the findings from the risk assessment will help to avoid overtreatment and unnecessary exposure to adverse events as well as undertreatment and suboptimal therapeutic benefit. Risk-adapted treatment, including consideration of disease attributes, line of therapy, and patient attributes, is essential to maximizing outcomes and quality of life (Figure 2). All patients should receive palliative and supportive care, which should be tailored to the individual patient and regimen and initiated at the time of diagnosis. Potential disease and treatment-emergent adverse events must be considered in the context of individual patient attributes when considering the risks associated with treatment (Table 3).

### TREATMENT OF NEWLY DIAGNOSED CHRONIC LYMPHOCYTIC LEUKEMIA

It is tempting to initiate treatment early in patients with CLL, given the number of newly developed agents with unique mechanisms of action and promising outcomes. However, there are no data to date to change the recommendations for treatment set forth by the International CLL-IPI Working Group (Table 2).

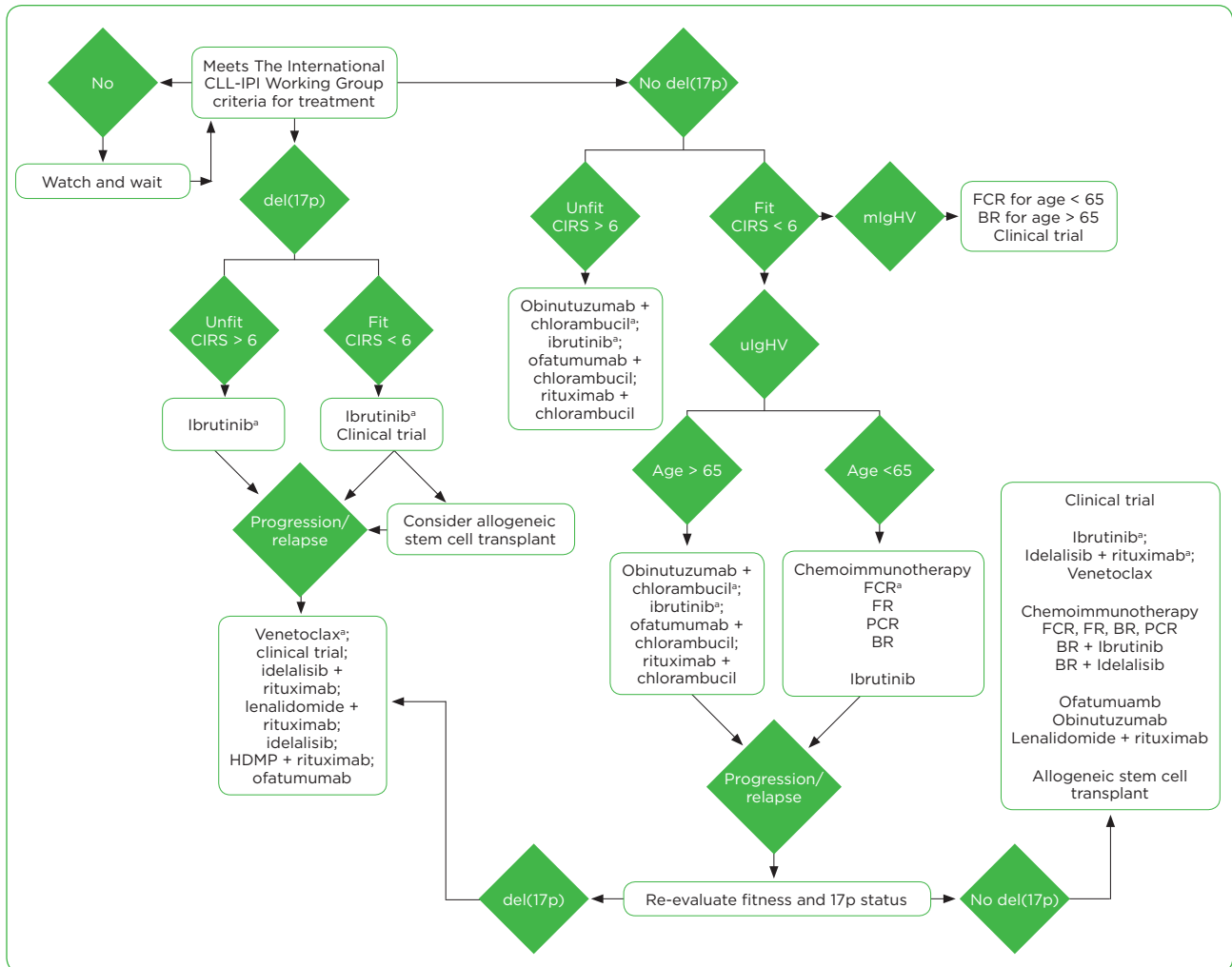
**Table 2. The Chronic Lymphocytic Leukemia International Prognostic Index (Training Cohort, n = 1,214)**

Prognostic factor	Adverse factor	Regression coefficient	Hazard ratio (95% CI)	p value	Weighted score
CLL FISH panel	17p deletion/ <i>TP53</i> mutation	1.434	4.2 (3.2–5.5)	< .0001	4
IgHV	Unmutated	0.950	2.6 (2.1–3.2)	< .0001	2
$\beta_2$ microglobulin concentration	> 3.5 mg/L	0.678	2.0 (1.6–2.4)	< .0001	2
Clinical stage	Rai I–IV or Binet B–C	0.464	1.6 (1.3–1.9)	< .0001	1
Age	> 65 years	0.555	1.7 (1.4–2.1)	< .0001	1
Risk category	Composite risk score	Patients (n = 1,214)	Median OS months (95% CI)	5-year OS (95% CI)	10-year OS (95% CI)
Low	0–1	341 (28%)	NR	93.2% (90.5–96.0)	79.0% (71.8–86.3)
Intermediate	2–3	474 (39%)	105 (96–119)	79.3% (75.5–83.2)	39.2% (31.0–47.4)
High	4–6	337 (28%)	75 (68–82)	63.3% (57.9–68.8)	21.9% (14.2–29.6)
Very high	7–10	62 (5%)	29 (18–40)	23.3% (12.5–34.1)	3.5% <sup>a</sup> (NE)

Note. CLL = chronic lymphocytic leukemia; FISH = fluorescence in situ hybridization; NR = not reached; NE = not evaluable; OS = overall survival. Information from International CLL-IPI Working Group (2016).

<sup>a</sup>At the time of the last observation (month 93).





**Figure 2.** Risk-adapted treatment of chronic lymphocytic leukemia. CIRS = Cumulative Illness Rating Scale; HDMP = high-dose methylprednisolone; uIgHV = unmutated immunoglobulin heavy-chain variable gene; mIgHV = mutated IgHV; FCR = fludarabine, cyclophosphamide, and rituximab; FR = fludarabine and rituximab; PCR = pentostatin, cyclophosphamide, and rituximab; BR = bendamustine and rituximab. <sup>a</sup>NCCN Category 1 designation.

Let's apply the metrics of risk assessment to three patients with previously untreated CLL.

### Case Study 1

Mrs. J is a 75-year-old female who presented to her primary care physician (PCP) 2 weeks ago with palpitations, progressive fatigue, and increased joint pain. She was noted to have an elevated white blood cell (WBC) count ( $96 \times 1,000/\mu\text{L}$ ), moderate anemia (hemoglobin [Hgb] 8.1 g/dL), and thrombocytopenia ( $97 \times 1,000/\mu\text{L}$ ). Flow cytometry on the peripheral blood confirms a diagnosis of CLL. A bone marrow biopsy is performed showing 90% involvement of the bone marrow by CLL, normal female karyotype,

normal FISH panel, ZAP-70–negative,  $\beta_2$  microglobulin 3.4 m/L, and mutated IgHV. A noncontrast computed tomography (CT) shows no significant adenopathy and no splenomegaly. She has a history of atrial fibrillation, chronic renal insufficiency (creatinine clearance [CrCl] 55 mL/min), and osteoarthritis. She is married and lives with her husband, who is relatively healthy. They walk with their dog daily.

#### Risk Assessment:

- Rai stage: III
- Cumulative Illness Rating Scale (CIRS) = 3
- CLL-IPI score: 2 (age > 65, Rai stage III) = intermediate risk
- The International CLL-IPI Working Group

criteria for treatment: Yes—progressive fatigue, cytopenias, fevers without infection

- Risk-adapted treatment selection: either a clinical trial or the combination of bendamustine plus rituximab

### Case Study 2

Mrs. R is a 72-year-old female who presented with recurring pharyngitis, low-grade fevers, progressive fatigue, adenopathy, abdominal pain, and > 10% weight loss. Her medical history includes hypertension, gastroesophageal reflux disease, hypothyroidism, cholelithiasis, shingles, exaggerated reaction to insect bites, and chronic pain due to a previous car accident. She was diagnosed with CLL 1 year ago based on peripheral blood analysis and has been monitored off treatment.

On a physical exam, she has extensive adenopathy in the cervical, axillary, and inguinal regions as well as palpable splenomegaly. Other diagnostic findings include: WBC count:  $230.7 \times 1,000/\mu\text{L}$ ; absolute lymphocyte count (ALC):  $223.78 \times 1,000/\mu\text{L}$ ; Hgb: 10.9 g/dL; platelets:  $180 \times 1,000/\mu\text{L}$ ; lactate dehydrogenase (LDH): 250 IU/L (upper limit of normal [ULN] 243),  $\beta_2$  microglobulin: 2.5 mg/L, ZAP-70–positive. A bone marrow biopsy is performed, showing 80% involvement with small mature noncleaved lymphocytes, metaphase cytogenetics with a normal female karyotype (46, XX [15]), and FISH with 17p13 deletion in 92/200 cells.

#### Risk Assessment:

- Rai stage: III (Hgb < 11 g/dL, splenomegaly, adenopathy, lymphocytosis)
- CIRS: 5
- CLL-IPI score: 8 (17p+, Rai stage I–IV, IgHV unmutated, age > 65) = very high risk
- The International CLL-IPI Working Group criteria for treatment: Yes—progressive fatigue, cytopenias, fevers without infection
- Risk-adapted treatment selection: either a clinical trial or ibrutinib (Imbruvica)

### Case Study 3

Mr. B. is a 75-year-old male diagnosed as Binet stage 0 CLL. His disease profile includes small to medium adenopathy (0.7 cm–2.7 cm), FISH with trisomy 11q, mutated IgHV (mIgHV). His medical history includes psoriasis, seasonal sinus infections, and benign prostatic hyperplasia (BPH). He

**Table 3. Indications to Initiate Treatment for Chronic Lymphocytic Leukemia**

Category	Indication for treatment
CLL-related symptoms	<ul style="list-style-type: none"> <li>• Significant B symptoms (e.g., night sweats, fever without infection, severe fatigue, unintentional weight loss)</li> </ul>
Tumor burden	<ul style="list-style-type: none"> <li>• Massive nodes (e.g., 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy</li> <li>• Massive (e.g., 6 cm below the left costal margin) or progressive or symptomatic splenomegaly</li> <li>• Progressive lymphocytosis with an increase of &gt; 50% over a 2-month period</li> <li>• Lymphocyte doubling time &lt; 6 months (if ALC &gt; <math>30 \times 10^9/\text{L}</math>)</li> <li>• Threatened end-organ function (e.g., enlarged lymph node obstructing bowel)</li> <li>• Richter's transformation</li> </ul>
Bone marrow failure	<ul style="list-style-type: none"> <li>• Progressive anemia (Hgb &lt; 11 mg/dL)</li> <li>• Progressive thrombocytopenia (Plt &lt; 100K)</li> </ul>
Immune dysfunction	<ul style="list-style-type: none"> <li>• Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy</li> </ul>

Note. ALC = absolute lymphocyte count; Hgb = hemoglobin; Plt = platelets. Information from Hallek (2015).

is here for a scheduled follow-up visit. Labs: WBC ( $25.5 \times 1,000/\mu\text{L}$ ); ALC  $18.62 \times 1,000/\mu\text{L}$ ; normal  $\beta_2$  microglobulin, and no cytopenias. He does report fatigue, but this has not changed. He is recently widowed and is depressed.

#### Risk Assessment:

- Rai stage: 0 (asymptomatic)
- CIRS: 1
- CLL-IPI score: 1 (age > 65) = low risk
- The International CLL-IPI Working Group criteria for treatment: No—he has no indications to treat
- Risk-adapted treatment selection: surveillance/watch and wait

### Discussion

These case studies illustrate the significance of a comprehensive risk assessment to determine the need for treatment and the selection of therapy. The patient in case study 3 does not meet the International CLL-IPI Working Group criteria for treat-

**Table 4. Common Adverse Events Associated With FDA-Approved Oral Agents for Chronic Lymphocytic Leukemia Based on Prescribing Information**

Adverse event (%) (Alphabetical order)	Ibrutinib		Idelalisib		Venetoclax	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
ALT/AST elevation	NR	NR	28-39	11-18 # !	NR	NR
Anemia	33-46	0	NR	NR	29	18
Anorexia	21	2	16	2	NR	NR
Arthralgia/myalgia	16-59	0-2	9	1	10	< 1
Atrial fibrillation	6-16	2-6 #	NR	NR	NR	NR
Bleeding/hemorrhage	44-69	0-6 #	NR	NR	NR	NR
Bruising	20-26	0-2	NR	NR	NR	NR
Colitis	NR	NR	-	14-19 !	NR	NR
Contraindications	None		History of serious allergic reactions		Concomitant use of strong inhibitors of CYP3A at initiation and during ramp-up	
CYP3A interactions	Yes		Yes		Yes	
Diarrhea	36-59	4	32	11 # !	35	< 1
Dose modification	Hepatic/hematologic		Hepatic/hematologic		Hepatic/hematologic/TLS	
Edema	8-29	0-1	NR	NR	11	< 1
Embryofetal toxicity	Possible #		Possible #		Possible #	
Fatigue/lethargy	5-30	0-5	5	0	21	2
Hypertension	11-16	4-8 #	NR	NR	NR	NR
Infections	See pneumonia/URI		5-9	21-36 !	See pneumonia/URI	
Intestinal perforation	NR	NR	Reported		NR	NR
Lymphopenia	NR	NR	21	10	NR	NR
Nausea	16-20	0-2	30	1	33	< 1
Neutropenia	4-24	0-5 #	65	42	45	41 #
Pneumonia/URI	10-26	4-20 #	30	21	30	6
Pneumonitis	NR	NR	-	4 !	NR	NR
Rash	3-47	0-3	27	4	NR	NR
Sepsis	NR	NR	NA	9	NR	NR
SPM	3-16	NA	NR	NR	NR	NR
Laboratory TLS <sup>+</sup>	Rare; #	0	NR	NR	6	6 #
Thrombocytopenia	16-21	5-10 #	NR	NR	22	15

*Note.* FDA = US Food and Drug Administration; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported; # = warning and precautions; ! = black box warning; URI = upper respiratory infection; SPM = secondary primary malignancies; TLS = tumor-lysis syndrome; + = using ramp-up dosing of venetoclax. Information from AbbVie (2016); Gilead (2017); Pharmacyclics (2016).

ment. Although he has the del(11q), a higher-risk feature, this alone does not indicate the need for treatment (International CLL-IPI Working Group, 2016). The patients in case study 1 and 2 meet the International CLL-IPI Working Group criteria to

initiate treatment; however, the preferred regimen for treatment in each case is very different.

In case study 1, the patient has mIgHV, with intermediate-risk disease. Patients with mIgHV in the absence of any other adverse risk factors

may enjoy a longer time to treatment initiation. In addition, once treated with fludarabine, cyclophosphamide, and rituximab (FCR), these patients may experience long-term remissions and may in fact be potentially cured of their disease (Fischer et al., 2016; Thompson et al., 2016). This patient is older and does have comorbidities, which would increase the risk associated with FCR. Patients who are not candidates for this more intensive chemoimmunotherapy may benefit from bendamustine and rituximab (BR).

In the phase III CLL 10 trial comparing front-line BR and FCR in 561 patients with a CIRS < 6 and CrCl > 70 mL/min, without del(17p), median PFS was 41.7 months (95% confidence interval [CI] = 34.9–45.3) with bendamustine and rituximab and 55.2 months (95% CI not evaluable) with FCR (HR, 1.643, 90.4%; CI = 1.308–2.064) at 37 months of follow-up (Eichhorst et al., 2016). Objective response rate (ORR) was equivalent in each treatment group (95.4 vs. 95.7%;  $p = 1.0$ ); however, patients in the FCR group were significantly more likely than those treated with BR to achieve a complete response (39.7 vs. 30.8%;  $p = .034$ ). No differences in OS between the FCR and BR groups were noted at 36 months of follow-up (90.6 vs. 92.2%;  $p = .897$ ). Adverse events, including severe neutropenia and infections, were more frequently observed with FCR when compared with BR, and serious infections were more common in patients over the age of 65 receiving FCR (Eichhorst et al., 2016). Therefore, FCR is not recommended for older or frail patients.

The patient in case study 2 has very high-risk disease, with a CLL-IPI score of 8. The presence of del(17p) accounts for 4 points alone. Standard chemoimmunotherapy is not effective in patients with del(17p). There are only two agents approved for treatment specifically in the presence of del(17p), including ibrutinib and venetoclax (Venclexta). Alectuzumab has established activity in this setting but is no longer commercially available for treatment of CLL; however, it can be obtained for clinical use. It is not effective in patients with bulky disease and is associated with a higher risk of reactivation of cytomegaloviral infections (Wierda et al., 2017).

### Ibrutinib

Ibrutinib, a first-in-class Bruton's tyrosine kinase (BTK) inhibitor, has a broad indication in the treat-

ment of CLL in treatment-naïve (TN), relapsed or refractory (RR), and del(17p) CLL patients as well as those over the age of 65 (Foluso, Glick, Stender, & Jaiyesimi, 2016; Maddocks & Jones, 2016). It was first approved in February of 2014 as a single agent for treatment of patients with CLL after one prior therapy (Byrd et al., 2013, 2014). Continued clinical trials using ibrutinib as a single agent and in combination with BR led to its expanded approval for use in the front-line setting, including for older patients (Burger et al., 2015; O'Brien et al., 2014), and in combination with BR in patients with RRCLL (Chanan-Khan et al., 2016).

Among the 656 CLL patients participating in these trials, the ORR ranged from 63% to 88% in RRCLL and 97% in TN CLL, including patients with del(17p), 11q, and uIGHV (Farooqui et al., 2015; Foluso et al., 2016; Jain et al., 2017). Although response rates and PFS outcomes in these trials are promising, complete responses were rare, indicating a need to explore other novel combinations (Jain et al., 2017). Several trials are underway evaluating these novel combinations as well as second-generation BTK inhibitors (Table 5).

Recent publications evaluating long-term outcomes for CLL patients treated with ibrutinib in both TNCLL and RRCLL have elucidated several important points: (1) Uncontrolled adverse events continue to be a leading cause of treatment discontinuation—the most common adverse events cited for early discontinuation of ibrutinib included atrial fibrillation, infection, pneumonitis, bleeding, and diarrhea (Barr et al., 2016; Byrd et al., 2017; Jain et al., 2017; Mato, 2016); (2) Adverse-event profiles in the postmarketing setting are mostly consistent with profiles reported in the clinical trials, with some variations in frequency and severity in patients on long-term treatment including persistent hypertension and the incidence of atrial fibrillation and bleeding episodes (Barr et al., 2016; Gashonia et al., 2017; Kunk et al., 2016; Mato et al., 2016; Shanafelt et al., 2017; Yun, Vincelette, Acharya, & Abraham, 2017); (3) Patients who discontinued ibrutinib due to progression of disease may benefit from other small-molecule agents; however, those who progress with Richter's transformation have an extremely poor prognosis, with an estimated life expectancy of 1.5 years (Mato et al., 2016).

**Table 5. Selected Clinical Trials Currently Recruiting Using Novel Agents for the Treatment of Chronic Lymphocytic Leukemia**

Trial ID	NCT #	Regimen	CLL population	Phase
CLL12	NCT02863718	Ibrutinib vs. watch and wait	TN Binet stage A	III
E1912	NCT02048813	FCR + ibrutinib vs. ibrutinib + rituximab	Young, fit, TN	-
A041202	NCT01886872	BR vs. ibrutinib + rituximab	65 years or older, TN	-
150172	NCT02514083	Ibrutinib + short-course fludarabine	Fit, TN	II
CLL2-GIVE	NCT02758665	Ibrutinib + venetoclax + obinutuzumab	Fit, TN, with <i>TP53</i> deletion (17p-) and/or mutation	II
CLL13	NCT02950051	FCR/BR vs. rituximab + venetoclax vs. obinutuzumab + venetoclax vs. obinutuzumab + ibrutinib + venetoclax	Fit, TN, no del(17p) nor <i>TP53</i> mutation	III
CLL2-BIO	NCT02689141	Bendamustine followed by ofatumumab and ibrutinib followed by ibrutinib and ofatumumab maintenance	All-comer population with indication for treatment	II
CLL2-BCG	NCT02445131	Bendamustine followed by obinutuzumab + idelalisib followed by idelalisib maintenance	All-comer population with indication for treatment	II
UTX-TGR-304	NCT02612311	Ublituximab + TGR-1202 vs. obinutuzumab + chlorambucil	TN or RR, no prior obinutuzumab, PI3K, or chlorambucil	III
CLLR3	NCT02320383	Fludarabine + cyclophosphamide + obinutuzumab vs. bendamustine + obinutuzumab	Fit, RR, no more than 3 prior regimens for CLL	II
MDA 2015 0860	NCT02756897	Venetoclax + ibrutinib	TN with high-risk features RR	II
141106	NCT02315768	Ibrutinib + obinutuzumab	All-comer population with indication for treatment	I/II
ACE-CL-208	NCT02717611	ACP-196 (acalabrutinib)	RR	II

*Note.* TN = treatment naive; FCR = fludarabine, cyclophosphamide, and rituximab; BR = bendamustine and rituximab; RR = relapsed refractory; PI3K = phosphoinositide 3-kinase. Information from [clinicaltrials.gov](http://clinicaltrials.gov).

Pretreatment risk assessment is critical to mitigating risks and should include collaboration with co-managing providers such as PCPs and cardiologists to reduce potential drug-drug interactions and optimally manage expected adverse events. Factors shown to correlate with an increased risk of treatment-emergent atrial fibrillation include older age ( $\geq 75$  years), male sex, valvular heart disease, and hypertension (Shanafelt et al., 2017; Yun et al., 2017). Anticoagulation, a proven method for reducing the potential for ischemic stroke in the setting of atrial fibrillation, can be safely managed in CLL patients receiving ibrutinib but requires vigilance and engagement of the patient in early reporting of adverse events and maintaining safety (Yun et al., 2017). Infections, particularly sinopulmo-

nary infections, are common in the general CLL population. Atypical infections are also more common in CLL, owing to chronic immunosuppression associated with the disease and treatment. Vigilance in monitoring and methods to prevent atypical infections is recommended.

### Oral Adherence

Based on the mechanism of action, the current recommendation for all small molecules, including ibrutinib, is to continue treatment until disease progression or unacceptable toxicity. Although scientifically sound, this principle presents many potential barriers to younger patients with a life expectancy of more than a couple of years, including adherence and unknown long-term toxicities (Barrientos, 2016). Oral ad-

herence is a continuous challenge across cancer diagnoses. Patients missing  $\geq 8$  consecutive days of ibrutinib had a shorter median PFS than did those missing  $< 8$  days (10.9 months vs. not reached; Barr et al., 2017).

Drug-drug interactions are common with small-molecule agents used to treat CLL and may either increase the risk of treatment-emergent adverse events, reduce the efficacy of novel agents, or modify the safety and efficacy of concomitant medications (Finnes et al., 2016).

A recent study evaluating perceptions of adherence communication and actual adherence in patients with CLL (81 physicians and 326 patients) showed a disparity between what physicians reported (87% indicated their CLL patients were “always” or “almost always” adherent) and patients reported (42% of patients reported they were “never” or “hardly ever” nonadherent to CLL treatment; Schneckel, Hallworth, Rider, Macomson, & McRae, 2017).

The advanced practitioner in oncology plays a pivotal role in communication with the patient and among the interprofessional team. Establishing a program and process for support of patients on oral antineoplastic agents, including evaluation and management of possible drug-drug or drug-food interactions, is essential to safety and continued treatment with novel agents.

### Monoclonal Antibodies

Monoclonal antibodies, including obinutuzumab (Gazyva), ofatumumab (Arzerra), and rituximab, provide a cadre of well-tolerated options for treatment of CLL in the front-line or RR setting (Chaoui et al., 2017; Wierda et al., 2017; Figure 2). They have become a mainstay in the treatment of lymphoid malignancies. Although they have limited benefit as single agents, when combined with standard chemotherapy (bendamustine, chlorambucil, fludarabine, cyclophosphamide), they provide safe and effective options for treatment with well-known and acceptable adverse events (Table 6). More recently, monoclonal antibodies are being combined with novel agents, with early data suggesting these “no chemotherapy required” regimens as feasible options for the treatment of CLL in the front-line, RR, and maintenance settings (Wierda et al., 2017; Table 5).

## TREATMENT OF RELAPSED OR RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Treatment of RRCLL requires re-evaluation of both patient- and disease-related factors. Analysis of prior therapies, response and tolerance of the prior therapies, any new or unresolved adverse events, and the presence of any acquired adverse disease features is essential. Let’s consider a patient with RRCLL.

### Case Study 4

Mr. C is a 47-year-old male with a 10-year history of Rai stage I CLL with del(13q), ZAP-70–negative, normal  $\beta_2$  microglobulin, and mutated IgHV at the time of diagnosis. He was previously treated with six cycles of FCR, achieving a complete response. It has been 7 years since his treatment. He presents to clinic with a new cervical lymph node, increased fatigue, abdominal pain, intermittent diarrhea, and shortness of breath when he bends over. His WBC count is  $47 \times 1,000/\mu\text{L}$  with lymphocytosis, mild anemia (Hgb 11.2 g/dL), and a platelet count slightly below normal ( $137 \times 1,000/\mu\text{L}$ ).

On physical exam, you note an enlarged spleen. Computed tomography scan of the chest, abdomen, and pelvis shows moderate splenomegaly and scattered adenopathy, with the abdomen with the largest nodal conglomerate in the mesentery (measuring 5.8 cm in greatest dimension). The FISH analysis shows the presence of del(17p). He has no other medical or surgical history. He is married, working full time, and has two children. He denies night sweats or unexplained weight loss.

#### Risk Assessment:

- CIRS: 0
- CLL-IPI score: 5
- The International CLL-IPI Working Group criteria for treatment: Yes
- Risk-adapted treatment selection: clinical trial, ibrutinib or venetoclax followed by allogeneic stem cell transplant

In patients who relapse more than 3 years after treatment with FCR or BR, repeating those regimens may be reasonable unless they have acquired del(17p) (Barrientos, 2016). The patient in case study 4 was treated more than 3 years ago with FCR and enjoyed a time-to-treatment interval of 7 years. However, he has an

**Table 6. Common Adverse Events Associated With FDA-Approved Monoclonal Antibodies for Chronic Lymphocytic Leukemia**

Adverse event (%) (Alphabetical)	Obinutuzumab		Ofatumumab		Rituximab	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
ALT/AST elevation	28	2	NR	NR	NR	NR
Anemia	39	10	NR	NR	8	3
Arthralgia/myalgia	12	0	5	< 1	10	1
Contraindications	None		None		-	
Cough	26	0	NR	NR	13	1
Diarrhea	10	2	NR	NR	10	1
Edema	NR	NR	NR	NR	11	1
Embryofetal toxicity	Possible		Possible		Possible	
Fatigue/lethargy	11	1	8	< 1	26	1
Hepatitis B reactivation	Possible !		Possible !		Possible !	
Hypoalbuminemia	23	< 1	5	< 1	-	
Immunizations	Do not administer live virus vaccines		Do not administer live virus vaccines		Do not administer live virus vaccines	
Infusion reactions	66	20 #	67	10 #	77	10 #
Lymphopenia	84	35	52	29	48	40
Mucocutaneous reactions/ bowel perforation or obstruction	NR	NR	NR	NR	Reported !	
Nausea	NR	NR	NR	NR	23	1
Neutropenia	76	46 #	27	26 #	14	6
PML	Possible !		Possible !		Possible !	
TLS	Possible #		NR	NR	Possible #	
Thrombocytopenia	48	13 #	NR	NR	12	2
URI/pneumonia/sinus	15	3	36	6	31	4

*Note.* FDA = US Food and Drug Administration; ALT = alanine aminotransferase; AST = aspartate aminotransferase; # = warning and precautions; ! = black box warning; NR = not reported; URI = upper respiratory infection; PML = posterior multifocal leukoencephalopathy; TLS = tumor-lysis syndrome. Information from Genentech (2016); Genentech (2017); Novartis (2017).

acquired del(17p), which changes his risk profile and the recommendation for treatment. Clonal evolution, the acquisition of new cytogenetic abnormalities during the disease course, is thought to drive CLL relapse and has implications for OS (Roberts & Huang, 2017; Woyach et al., 2014). The acquisition of high-risk abnormalities, particularly del(17p), is associated with inferior OS, whereas the acquisition of low- or intermediate-risk abnormalities (trisomy 12, deletion 13q) does not independently change the estimated OS. Therefore, all patients should be re-evaluated for

acquired adverse-risk features and their level of fitness at the time of relapse or disease progression to effectively guide treatment decisions.

For this patient, a clinical trial with the endpoint being allogeneic stem cell transplant would be ideal. Alternatively, a regimen that incorporates agents with proven efficacy in patients with del(17p) CLL, either ibrutinib or venetoclax, as a bridge to transplant is optimal. Ibrutinib has been previously discussed in detail. Older or less fit patients, or those without del(17p), may be considered for alternative regimens (Figure 2).

Idelalisib (Zydelig), a first-in-class, oral, selective, phosphoinositide 3-kinase (PI3K)  $\delta$  inhibitor, was approved for the treatment of relapsed SLL in patients who have received at least two prior systemic therapies and for the treatment of relapsed CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy because of other comorbidities (Gilead, 2016). Approval of idelalisib was based on a phase III randomized trial in a primarily older patient population (78% age > 65) with comorbidities (85% with CIRS > 6). Idelalisib offers a good option for selected patients in the second-line setting but must be balanced with a toxicity profile that includes a black box warning for fatal and severe hepatotoxicity, diarrhea or colitis, pneumonitis, and intestinal perforation (Gilead, 2016; Table 4). Ongoing trials are evaluating idelalisib in combination with monoclonal antibodies with and without novel agents (Table 5). Given the goal of transition to stem cell transplant and the risk of infections and gastrointestinal toxicity, this would not be the first choice of treatment in this young patient.

Venetoclax, a first-in-class small-molecule inhibitor of BCL2, is approved for the treatment of patients with CLL with 17p deletion, as detected by an FDA-approved test, who have received at least one prior therapy (AbbVie, 2016). Approval of venetoclax was based on data from phase I and II trials, with 79% of all patients in both trials achieving an objective response, regardless of the dose of venetoclax (Roberts & Huang, 2017). In addition, 20% of patients in these trials achieved a complete response, including patients with a del(17p) deletion. Although minimal residual disease (MRD) status was not included in the initial evaluation, a subset of patients achieved MRD-negative status.

Like other small-molecule agents, venetoclax has adverse events that require risk assessment and measures for prevention (Table 4). Tumorlysis syndrome (TLS) is included in the warnings and precautions. Two fatal events and three cases of acute renal failure, with one requiring dialysis, were reported in the initial phase I trial. Subsequent modification of the dosing using a ramp-up method, together with guidelines for evaluation of TLS risk, prevention, and management, resulted in only 6% of patients on the phase II trial

reported as having laboratory TLS. No cases of clinical TLS were noted (Roberts et al., 2016). The time to response with venetoclax is rapid, ranging from 0.1 to 8.1 months. Therefore, careful assessment of the risk of TLS prior to initiating therapy is required for safety. Patients at higher risk require inpatient administration of venetoclax and more intensive prevention and monitoring with the initial ramp-up. These guidelines can be found in the prescribing information for venetoclax and are also included in the National Comprehensive Cancer Network® Guidelines. As with other novel agents used in the treatment of CLL, venetoclax is being combined with other agents in ongoing clinical trials.

## CONCLUSIONS

Chronic lymphocytic leukemia is a heterogeneous disease with variability in prognosis, disease trajectory, and survival. This is primarily a disease of older adults. The robust pace of scientific development has improved our understanding of the underlying pathobiology of the disease and has elucidated actionable targets to produce novel therapies, ultimately expanding treatment options and in many cases improving therapeutic outcomes. None of these agents would be available in the absence of clinical trials. Therefore, every patient should be considered for a clinical trial regardless of the stage of disease or the line of therapy.

Treatment after failure of novel agents presents a challenge. Emerging trials using novel agents in rational combinations based on their mechanism of action, signaling pathways, and targets offer hope in generating therapies that more effectively exploit the vulnerabilities in CLL cells and their microenvironment. This will require lifelong learning on the part of all oncology professionals.

Safe and effective integration of these new therapies presents a challenge for the advanced practitioner in oncology. Risk assessment and prognostication followed by risk-adapted treatment selection will promote selection of the best available therapy and limit overtreatment of patients who are unfit. The ability to anticipate, prevent, and identify adverse events, and then intervene promptly to mitigate risk, is critical to maximizing outcomes. Understanding the unique toxicity profiles of novel



therapies and integrating this into risk-adapted treatment selection is critical to mitigating this risk.

### SPECIAL NOTE: PRIMING THE PUMP

Condensing the plethora of scientific advances and implications for clinical practice into one article is impossible, and not all agents, regimens, or clinical trials have been reviewed. The Advanced Practitioner Society for Hematology and Oncology (APSHO) has embarked on a new educational and practice initiative entitled “Priming the Pump” (PTP). The PTP initiative is aimed at creating and maintaining an intuitive and interactive foundation of knowledge relative to emerging therapies. This initiative will include several comprehensive supplements to JADPRO, each focusing on a different disease state, covering discussion of the disease, relevant therapeutic pathways, targets, and treatment options, with the role of the advanced practitioner always at the core.

The PTP supplement on CLL, to be published at the end of this year, will provide a comprehensive review of the pathobiology of CLL, diagnostic evaluation, risk-adapted treatment selection, management of adverse events, and discussion of ongoing clinical trials and emerging agents. ●

### Disclosure

Ms. Kurtin has served as a consultant for AbbVie, Celgene, and Genentech. Dr. McBride has served on the speakers bureau for AbbVie.

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