# JADPRO Clinical Case Series

# **Managing CLL Patients Receiving BTK Inhibitor Treatment:**

Considerations for Advanced Practitioners

# PRESENTER

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# Objectives

- Understand the role of new oral targeted therapies in the treatment of chronic lymphocytic leukemia (CLL), and the management of patients taking these medications
- Review case studies to gain a better understanding of treatment decision-making in CLL, and the role of a multidisciplinary team approach in managing patients on their treatment journey

# Evolving Treatment Landscape for CLL: Focus on BTK Inhibitors

**Prior to 2014**

"One-size-fits-all" chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab (FCR)[1]

**2015**

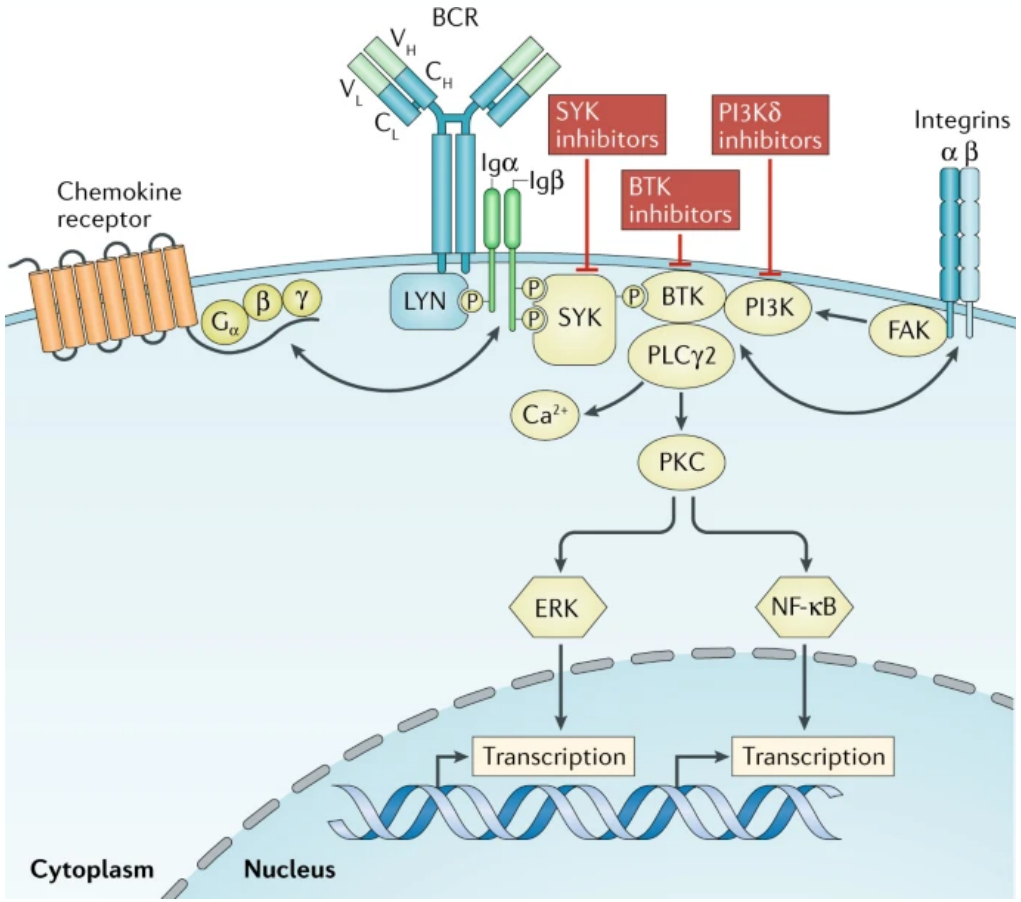
**Ibrutinib** approved as first oral targeted therapy, targeting the BTK protein within the B-cell receptor (BCR) signaling pathway[2]

**2019**

**Acalabrutinib** approved as a second-generation BTK inhibitor with greater specificity and fewer off-target effects[3]

1. Burger JA, O'Brien S. *Nat Rev Clin Oncol*. 201;15:510-527. 2. de Claro RA, et al. *Clin Cancer Res*. 2015;21:3586-3590. 3. Isaac K, Mato AR. *Cancer Manag Res*. 2020;12:2079-2085.

# BCR Signaling Pathway




Burger JA, O'Brien S. *Nat Rev Clin Oncol*. 201;15:510-527.

# AEs Associated With BTK Inhibitors

**Ibrutinib**[1,2] → **RESONATE-2 trial**

**Previously treated CLL**
- Median duration of treatment 65.3 mo
  - 41% receiving >4 years of therapy
- **Grade ≥3 AEs**
  - Cytopenias (9%-25%), pneumonia (21%), UTI (7%), diarrhea (7%), AF (6%), hemorrhage (10%)

**Acalabrutinib**[3] → **ELEVATE-TN trial**

**Treatment-naive CLL**
- Median duration of treatment 27.7 mo
- **Grade ≥3 AEs**
  - Cytopenias (3.4%-13%), infection (14%), hemorrhage (1.7%), headache (1.1%), musculoskeletal pain (1.1%), fatigue (1.1%)

AE, adverse event; AF, atrial fibrillation; UTI, urinary tract infection

1. Byrd JC et al. *N Engl J Med.* 2014;371:213-223. 2. Munir T et al. *Am J Hematol*. 2019;94:1353-1363. 3. Sharman JP et al. *Lancet.* 2020;295:1278-1291.

# Case 1: Nancy

- Diagnosed with CLL in 2016 at age 63
  - 13q and *TP53* deletions by FISH, and unmutated *IgHV*

**At diagnosis:**

- Asymptomatic
- Rai 1
- Bilateral axillary lymph nodes palpable at 2x2 cm

**CBC**

WBC, 35

Hgb, 13.2 g/dL

Platelets, 260 x $10^9$/L

**PMH**

Hypertension: taking lisinopril

Depression with anxiety

Hypercholesterolemia: taking simvastatin

Postoperative paroxysmal atrial fibrillation (AF)

CBC, complete blood count; Hgb, hemoglobin; PMH, past medical history; WBC, white blood cell

# Case 1: Indications for Treatment

**11/2019**

- Progressive adenopathy (axillary lymph nodes palpable at 4x4 cm), palpable splenomegaly (5 cm below costal margin), and increasing fatigue
- BMA/Bx: CLL at 70% of marrow cellularity
- Repeat FISH: 13q and TP53 deletions
- CT scan: splenomegaly and multicompartmental adenopathy with retroperitoneal lymph nodes up to 4.4 cm

**CBC and Lipids**

WBC, 94

Hgb, 11.1 g/dL

Platelets, 227 x $10^9$/L

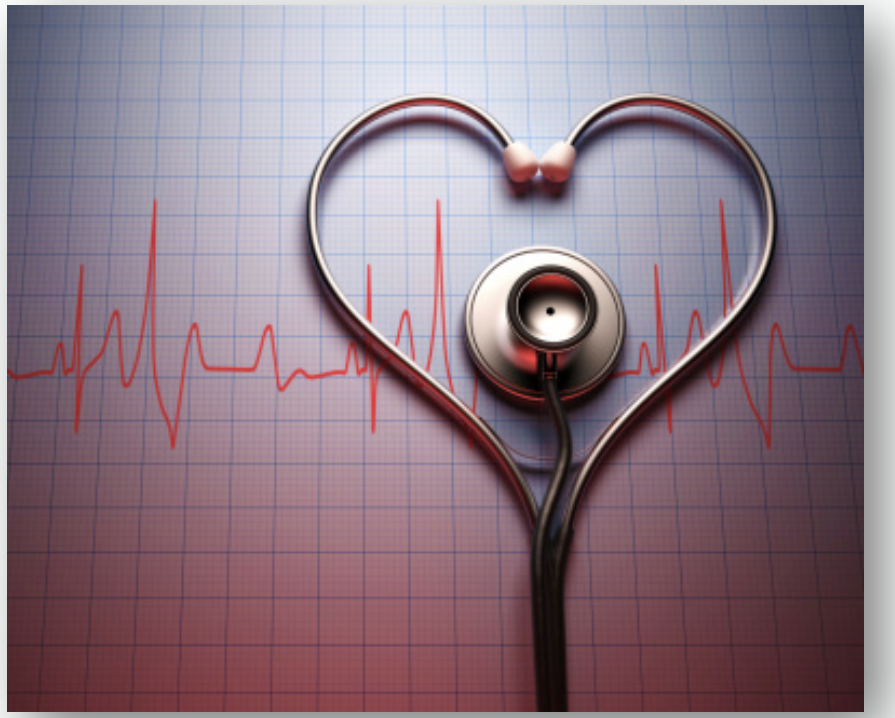
Total cholesterol, 189 mg/dL

LDL-C, 148 mg/dL

BMA/Bx, bone marrow aspiration/biopsy; LDL-C, low density lipoprotein cholesterol

# Case 1: Pretreatment Referral to Cardio-oncology

- Pretreatment cardiology
  - BP, 142/86 mm Hg
  - Echocardiogram, EF of 60%
  - ECG, normal sinus rhythm
  - Stress test, within normal limits
- Hypertension regimen was optimized with the addition of a diuretic (hydrochlorothiazide, 25 mg daily)



BP, blood pressure; ECG, electrocardiogram; EF, ejection fraction

# Case 1: First-Line CLL Treatment

- Acalabrutinib (100 mg BID) was recommended by her oncologist
  - Due to borderline cardiac risk factors

**By week 5 of treatment**

- Complete resolution of palpable adenopathy and splenomegaly

**By 6 months of treatment**

- CBC showed partial response
- Follow-up with cardio-oncology
  - BP, 136/74 mm Hg
  - Normal sinus rhythm on ECG
  - Lipid panel within normal limits

**6-mo CBC**

WBC 13.5

Hgb 12.2 g/dL

Platelets 238 x $10^9$/L

# Case 1: Polling Question

When would you consult cardio-oncology or cardiology for patients undergoing treatment with targeted oral oncolytics?

A. For all patients prior to starting oral oncolytic treatment **8%**

B. For patients with high-risk cardiac features (such as uncontrolled hypertension, history of dysrhythmia, etc.) prior to starting oral oncolytic treatment **62%**

C. For patients with any cardiac-risk features (e.g., diabetes, controlled hypertension, etc.) **17%**

D. At the first sign of any potential cardiotoxicity from treatment **12%**

E. Only if they are not already established with an outside cardiologist **0%**

# Case 2: Allan

- 74-year-old male diagnosed with CLL in 2001 at age 52 and first seen at MD Anderson in 2005
  - No mutations by FISH and hypermutated *IgHV* (3.4%)

**Developed indications for treatment in 2007**

- Progressive fatigue and night sweats

**Treated with FCR**

- Received 3 cycles of FCR, achieving MRD-negative CR
- Treatment was discontinued following C3 due to reactivation of CMV

**CBC**

WBC, 163.9

Hgb, 11.9 g/dL

Platelets, 128 x $10^9$/L

Beta-2-microglobulin (B2M), 4.4 mg/L

CMV, cytomegalovirus; CR, complete response; MRD, minimal residual disease

# Case 2: Additional Lines of Therapy

**2013**

Early evidence of relapse with lymphocytosis

**10/2019**

Developed indications for treatment: progressive cytopenias, increased fatigue, and drenching night sweats

**2014**

- Developed CNS blastomycosis, requiring placement of VP shunt
- Treated with voriconazole for 1 year
- Maintained on fluconazole and levetiracetam prophylaxis long-term

**CBC**

WBC, 59.5

Hgb, 9.4 g/dL

Platelets, 69 x $10^9$/L

**FISH, NGS**

13q deletion

Mutations in *ATM*, *MUC2*, *MYD88*, and *XPO1*

# Case 2: Medication Counseling

**Prescribed ibrutinib 140 mg daily in 10/2019**
(dose reduced due to taking fluconazole)

- Enrolled in an oral chemotherapy compliance program, provided by the PharmD team, and received medication counseling prior to initiation of therapy
  - Advised to stop taking fish oil supplements while on ibrutinib
  - Followed weekly for 1 month by AP to monitor labs and assess for toxicities, then monthly thereafter

**Developed rash 3 weeks into treatment**

- Did not resolve with topical steroids
- AP prescribed topical steroids and referred him to dermatology
  - Skin biopsy suggested a non-specific drug reaction

# Case 2: Switch to Another Agent in Same Class

**Rash persisted with ibrutinib**

- CBC and CLL-related symptoms improved
- Rash became intolerable

**Transitioned to acalabrutinib on 12/2019**
(100 mg dose due to ongoing antifungal therapy)

- CBC and CLL-related symptoms remained improved
- PharmD performed pretreatment counseling
  - Discovered recent addition of OTC esomeprazole daily; was switched to famotidine and referred to a registered dietitian
- Continued monthly follow-ups with an APP
  - Developed headaches early on in his acalabrutinib treatment
  - APP helped him manage his symptoms and headaches resolved

**CBC 1/19/2021**

WBC, 11.3

Hgb, 12.3 g/dL

Platelets, 140 x $10^9$/L

# Case 2: Polling Question

Who in your practice conducts pretreatment counseling with patients, including a thorough evaluation of current medications and supplements that patients are taking to evaluate for contraindications?

A. PharmD **39%**
B. NP or PA **39%**
C. Clinic nurse **17%**
D. Physician **0%**
E. We do not regularly do pretreatment counseling **4%**

# Case 3: Bob

- 61-year-old male diagnosed with CLL in 2004 at age 45

**At diagnosis:**

- Presented with autoimmune hemolytic anemia
  - Completed a prednisone taper and 4 weekly doses of rituximab with resolution
  - FISH testing on peripheral blood was negative; *IgHV* unmutated at 0% deviation
- Developed indications for treatment by 8/2013 (age 54)
- Progressive bulky adenopathy, increased fatigue, and night sweats
  - BMA/Bx: 90% CLL involvement
  - PET scan (to r/o Richters) showed bulky multicompartmental adenopathy with max SUV of 4
- Still working full time as manager at a petrochemical plant.

**CBC**

WBC, 30.7

Hgb, 15.1 g/dL

Platelets, 163 x $10^9$/L

**FISH, NGS**

13q deletion

Mutation in *ATM*

# Case 3: Relapsed After Initial Treatment

**Started fludarabine/cyclophosphamide/rituximab (FCR) regimen on 8/15/2015**

- Completed 4 cycles with MRD-positive remission
- Further treatment held due to prolonged myelosuppression
- Observed until 3/2017

**Developed indications for treatment on 3/2017**

- Progressive adenopathy, splenomegaly, increasing fatigue, night sweats
  - CT scan: adenopathy up to 4.7 cm and splenomegaly at 17 cm

**Started treatment on ibrutinib, 420 mg daily**

**CBC (2/28/2016)**

WBC, 2.8

Hgb, 10.2 g/dL

Platelets, 70 x $10^9$/L

# Case 3: Developed Arthralgias

**Responded well to treatment with ibrutinib**

- Rapid reduction in adenopathy and improvement in symptoms
  - WBC rose initially, reaching 187 on 4/28/2017

**Arthralgias and muscle cramps develop 3 months into treatment**

- His team recommended acetaminophen and tonic water

**Arthralgias continued as of 9/2017**

- Interfering with his ability to perform his job
- 12/2017: ibrutinib was held for 2 weeks; brief steroid taper
  - Restarted ibrutinib at a reduced dose of 280 mg daily

# Case 3: Transitioned to Acalabrutinib

**Arthralgias persisted**

- Continued on ibrutinib with stable disease,
- Persistent complaints of arthralgias required additional dose-holds

**Transitioned to acalabrutinib on 12/2019**

- Restaging 2/3/2020
  - CT scan, stable, minimal adenopathy (<1.5 cm)
  - BMA/Bx, CLL at 40%-50% cellularity
  - NGS assay showed mutated *ATM* gene and FISH confirmed *ATM* deletion
- Arthralgia symptoms resolved

**CBC**

WBC, 14

Hgb, 13.1 g/dL

Platelets, 8.8 x $10^9$/L

# Case 3: Polling Question

For a patient experiencing simultaneous toxicity and response on therapy, what is your preferred course of action?

A. Switch to a medication with a different mechanism of action **0%**

B. Continue to try to manage toxicity through supportive care, since the therapy is working **45%**

C. Consider switching to a therapy with the same mechanism of action but different toxicity profile **36%**

D. Decrease the dose of the current therapy to manage the toxicity **18%**

# Conclusions

- Past medical history can significantly impact treatment choice
- Concomitant medications may impact therapeutic outcomes and must be discussed regularly
- Anti-cancer therapies with the same mechanism of action may have different toxicity profiles

**The Role of the AP**

✓ Elicit a thorough past medical history from new patients starting anti-cancer therapy

✓ Educate patients regarding toxicity profiles and efficacy of anti-cancer therapies

✓ Discuss medication interactions

✓ Manage side effects of anti-cancer therapy

# Q & A

Please type your questions for Jill Miller into the **question box** in the control panel.

# Thank You