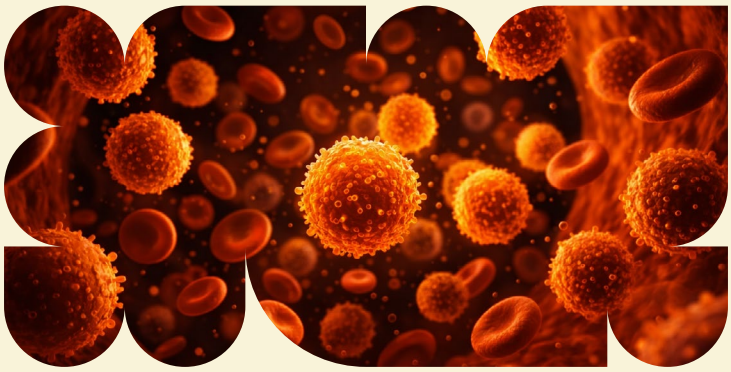
Nursing Considerations for Management of Chronic Lymphocytic Leukemia (CLL)

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- CLL is the most common type of leukemia in the Western world[1]
- Typically diagnosed by routine blood work
- Often asymptomatic and does not require immediate treatment; treatment is required for symptom management, cytopenias, or bulky lymphadenopathy

Guideline-Recommended First-line Therapy for CLL[1]

Without del(17)p/*TP53* mutation

Preferred Regimens:

- Acalabrutinib + venetoclax ± obinutuzumab (fixed duration)
- Venetoclax + obinutuzumab (fixed duration)
- Acalabrutinib ± obinutuzumab (continuous)
- Zanubrutinib (continuous)

Other Recommended Regimens:

- Ibrutinib + venetoclax (fixed duration or MRD guided)

Useful in Certain Circumstances

- Zanubrutinib + venetoclax (MRD guided)
- Ibrutinib (continuous)
- Ibrutinib (continuous) + rituximab or obinutuzumab
- HDMP + rituximab or obinutuzumab
- Consider only when cBTKi and BCL2i are not available or feasible
  - Bendamustine + rituximab or obinutuzumab
  - FCR
  - Chlorambucil + obinutuzumab
  - Obinutuzumab

With del(17)p/*TP53* mutation

Preferred Regimens:

- Venetoclax + obinutuzumab (fixed duration)
- Acalabrutinib + venetoclax + obinutuzumab (MRD guided)
- Zanubrutinib + venetoclax (MRD guided)
- Acalabrutinib ± obinutuzumab (continuous)
- Zanubrutinib (continuous)

Other Recommended Regimens:

- Ibrutinib + venetoclax (fixed duration)

Useful in Certain Circumstances

- Ibrutinib (continuous)
- HDMP + rituximab
- Consider only when cBTKi and BCL2i are not available or feasible
  - Obinutuzumab

Guidelines for Treatment of Relapsed/Refractory (R/R) CLL[1]

Prior BCL2i + anti-CD20 mAb
- BCL2i intolerance → cBTKi
- Relapse after response
  - BCL2i-containing regimen → cBTKi
  - cBTKi
- Progression on tx → cBTKi

Prior BCL2i + cBTKi ± anti-CD20 mAb
- BCL2i intolerance → cBTKi
- cBTKi intolerance → • BCL2i + alternate cBTKi • BCL2i ± anti-CD20 mAb
- Relapse after response → • BCL2i-containing regimen • cBKTi
- Progression on tx → ncBTKi

Prior cBTKi ± anti-CD20 mAb
- Intolerance
  - • Alternate cBTKi • ncBTKi → BCL2i-containing regimen
  - BCL2i-containing regimen → • Alternate cBTKi • ncBTKi
- Progression on tx → • BCL2i-containing regimen • ncBTKi

R/R after cBTKi or ncBTKi and BCL2i-containing regimen →
- Clinical trial
- CAR T-cell therapy
- ncBTKi (if not previously given)
- Other recommended regimens
- Consider allogeneic HCT

Shared Decision-making[2]



Finding the right treatment options will help optimize patient experience, drug adherence, and outcomes

Goals of Continuous- vs Fixed-Duration Therapy in CLL

Be prepared to review goals of care with patients and empower their decision-making

Goals of continuous therapy (eg, acalabrutinib, zanubrutinib)
- Disease control
- Prolonged PFS
- Independent from response, MRD

Goals of fixed-duration therapy (eg, venetoclax + obinutuzumab)
- Disease eradication
- Prolonged PFS
- Undetectable MRD

Common and Important BTK Inhibitor Toxicities in CLL[3]

Toxicities of Special Interest	Most Common Toxicities	Other Common Toxicities
AF	Anemia	Cytopenias
Ventricular arrhythmia	Arthralgia/myalgia	Hair/nail changes
Bleeding	Cough	Lymphocytosis
Hypertension	Diarrhea	Nausea
Infections	Fatigue	Rash
	Headache	
	Neutropenia	

Safety Considerations With Covalent BTK Inhibitors[4-8]

Acalabrutinib	Zanubrutinib
Head-to-head evidence shows fewer AF/flutter or hypertension events with acalabrutinib vs ibrutinib	Head-to-head data show fewer AF/flutter events with zanubrutinib vs ibrutinib
Headaches commonly occur early in therapy with acalabrutinib and typically resolve in 1-2 mo; manage with acetaminophen + caffeine	Neutropenia with zanubrutinib: For first occurrence, dose interruption is recommended
	Once toxicity has resolved to grade ≤1 or baseline, resume at 160 mg twice daily or 320 mg once daily
	Consider growth factor with G-CSF

Managing BTK Inhibitor Adverse Events[6,8-10]

AE	Management Strategy
Bruising and Hemorrhage	BTK inhibitor impact on platelet aggregation is often reversible within 1 wk of discontinuation **Recommendation:** Monitor patients for signs and symptoms of bleeding, including thrombocytopenia ○ Based on severity of bleeding: 1) reduce dose, 2) temporarily withhold, or 3) permanently discontinue BTK inhibitor • First occurrence of grade ≥3 thrombocytopenia with bleeding: hold dose, then restart at same initial dose if resolves to grade 1 or baseline • Second/third occurrence: hold dose and restart at the next lower dose level when AE resolves to grade 1 or baseline • Fourth occurrence or neutropenia lasting >7 days: permanently discontinue treatment Recommendation: Hold BTK inhibitor prior to and after invasive procedures for 3 days (minor) to 7 days (major) Inform patients that a blood thinner or antiplatelet agent may increase bleeding risk ○ Anticoagulants may increase bleeding risk by impacting multiple hemostatic pathways

AE	Management Strategy
AF and Cardiac Arrhythmias	◢ Risks include cardiac risk factors, acute infections, and prior history of AF ◢ **AF is not an absolute indication to discontinue BTK inhibitors; continued BTK treatment is reasonable with controlled AF** ◢ Cardiology consultation should be obtained before treatment if prior history of AF and when AF occurs during treatment ◢ Anticoagulation should be used with caution ◢ If grade ≥3 or AF persists, consider the risks and benefits of treatment and dose modification ◢ Monitor for signs and symptoms of arrhythmias (eg, palpitations, dizziness, syncope, dyspnea) and manage appropriately
Diarrhea	◢ Administer antidiarrheal agent (eg, loperamide) as needed
Headache	◢ Before treatment starts: Advise that headaches should lessen quickly, are easily managed, and are not a long-term treatment consequence ◢ After treatment starts: Recommend use of caffeine or acetaminophen; avoid NSAIDs
Hypertension	◢ Monitor for treatment-emergent hypertension ◢ Administer antihypertensive drug ◢ Reduce dose of antihypertensive drug once BTKi is stopped
Infection	◢ Consider prophylaxis for patients at increased risk of opportunistic infection ◢ Monitor for signs and symptoms ◢ Treat as needed
Musculoskeletal pain	◢ Grade 1 myalgias/arthralgias may not require intervention ◢ Dose reduction/interruption should be used as appropriate
Neutropenia	◢ 1st to 3rd occurrence of grade 3/4: Dose interruptions recommended ◢ 4th occurrence: BTK inhibitor discontinuation recommended
Thrombocytopenia	◢ 1st to 3rd occurrence of grade 3/4: Dose interruptions recommended ◢ 4th occurrence: BTK inhibitor discontinuation recommended (unless thrombocytopenia is related to CLL infiltration of bone marrow)

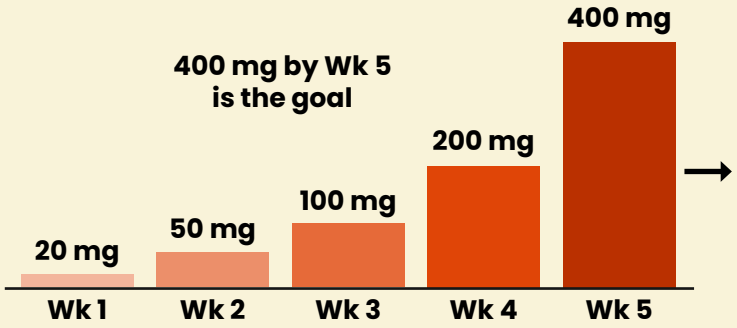
Patient and Caregiver Discussions: What AEs to Expect/Monitor While Taking BTK Inhibitors

- Initiate discussions with patients on what AEs can be expected while taking BTK inhibitors
- Tell patients that bruising and bleeding are expected to some degree while taking BTK inhibitors, particularly if engaging in physical activity and some daily tasks
- Tell patients to monitor for serious bleeding episodes in stools, blood in urine, or blood in sputum (coughing blood)
- Tell patients to notify their HCP of prolonged episodes of bruising and bleeding
- Recommend to patients that they carry a wallet card to let other HCPs know about the medication(s) they are taking and potential side effects and undesired DDIs (with antibiotics)
- Tell patients to notify their HCP of any new/planned medication or procedure
- Recommend no live vaccines, but inform that others like COVID-19, shingles, and seasonal flu are acceptable
- Discuss options for screening for more serious AEs (eg, cardiac arrhythmias/atrial flutter)

Dosing and Drug Interactions With Covalent BTK Inhibitors[6,8,9,11]

BTK Inhibitor Dosing in CLL	Coadministration With:			
	Strong CYP3A Inhibitors	Moderate CYP3A Inhibitors	Moderate or Strong CYP3A Inducers	Gastric Acid–Reducing Agents
Ibrutinib 420 mg once daily	Avoid use	Avoid use; if necessary, reduce to 280 mg once daily	Avoid use	No dosage adjustment recommended
Acalabrutinib maleate salt (IR film-coated tablet) 100 mg every 12 hr (capsules discontinued, transition to tablet)	Avoid use	Reduce to 100 mg once daily	Avoid use; if necessary, increase to 200 mg twice daily	Tablets can be used regardless of use of PPIs and ingestion of food
Zanubrutinib 160 mg orally twice daily or 320 mg orally once daily	Reduce to 80 mg once daily; interrupt dose for adverse events	Reduce to 80 mg twice daily; modify for adverse events	Avoid use	No dosage adjustment recommended

Venetoclax Dosing and Administration[12]



When used with a BTKi: Initiate venetoclax (according to 5-wk ramp-up dosing) cycle 3, Day 1

When used with obinutuzumab: Initiate venetoclax (according to 5-wk ramp-up dosing) cycle 1, Day 22

When used with rituximab: Start rituximab after the patient has completed venetoclax 5-wk ramp-up dosing and has received 400 mg once daily for 7 days

Venetoclax TLS Risk Stratification and Prophylaxis[12]

Prophylaxis

Low Tumor Burden
All LN <5 cm
AND
ALC <25 x 10^9/L

Medium Tumor Burden
LN 5 to <10 cm
OR
ALC ≥25 x 10^9/L

High Tumor Burden
Any LN ≥10 cm
OR
Any LN ≥5 cm AND ALC ≥25 x 10^9/L

Allopurinol 2-3 days prior and Oral hydration 1.5-2.0 L/day

Consider IV hydration if high risk

Add IV fluids 150-200 mL/hr

Consider rasburicase if hyperuricemic

TLS Monitoring

All doses outpatient

First 2 doses inpatient
- Labs at predose, 6-8 hr, 24 hr

Subsequent ramp-up doses
- Labs at predose

Consider treating as high burden if CrCl <80 mL/min

First 2 doses inpatient
- Labs at predose, 4 hr, 8 hr, 24 hr

Subsequent doses outpatient
- Labs at predose, 6-8 hr, 24 hr

Drug Interactions With Venetoclax[12]

Agents	Initiation and Ramp-up		Dose Reduction
Strong CYP3A Inducers • *Examples:* carbamazepine, phenytoin, rifampin, St John's wort	Avoid concomitant use		
Moderate CYP3A Inducers • *Examples:* bosentan, efavirenz, etravirine, modafinil	Avoid concomitant use		
Posaconazole (CYP3A Inhibitor)	D1: 10 mg D2: 20 mg	D3: 50 mg D4: 70 mg	Reduce venetoclax* to 70 mg
Other Strong CYP3A Inhibitor • *Examples:* clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, telaprevir, voriconazole	D1: 10 mg D2: 20 mg	D3: 50 mg D4: 100mg	Reduce venetoclax* to 100 mg
Moderate CYP3A Inhibitor • *Examples:* aprepitant, cimetidine, ciprofloxacin, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, verapamil	Reduce venetoclax* dose by ≥50%		
P-gp Inhibitor • *Examples:* amiodarone, carvedilol, cyclosporine, dronedarone, quinidine, ranolazine, verapamil	Reduce venetoclax* dose by ≥50%		
P-gp Substrate • *Examples:* digoxin, fexofenadine, loperamide, N-methyl-quinidine, quinidine, talinolol, vinblastine	If concomitant use is unavoidable, take at least 6 hr prior to venetoclax		

Venetoclax + Obinutuzumab Safety and Management[12,13]

Most common grade ≥3 AEs: Cytopenias, pneumonia, infusion-related reaction, TLS.[12]

AE	Management Strategy
TLS	• Assess risk for TLS → inpatient for first dose of first 2 ramp-up doses if high risk (ie, bulky adenopathy) • Prevent TLS with hydration and antihyperuricemic agents • Dose modification: withhold the next day's dose.; if resolved within 24-48 hr of last dose, resume at same or reduced dose • Treat per institutional guidelines
Neutropenia	• 1st occurrence of grade 3 with infection or fever or grade 4: interrupt dose until grade ≤1 and resume at same dose • Subsequent occurrences: interrupt dose and resume at reduced dose according to PI • Consider growth factor support
Diarrhea	• Administer antidiarrheal agent (eg, loperamide) as needed
Nausea	• Administer antiemetics as needed

Noncovalent BTK Inhibitors: Dosing and Safety of Pirtobrutinib[14,15]

Pirtobrutinib is approved for R/R CLL after previous treatment with a BTK inhibitor.

- Resistance to covalent BTK inhibitors is a driver of progressive disease/treatment discontinuation
- Patients with double-refractory CLL that has progressed with a covalent BTK inhibitor and venetoclax-based therapy historically have had poor outcomes
- Noncovalent BTK inhibitors represent a significant contribution to CLL care, can overcome BTK resistance, and are effective in double-refractory disease

Dosing

200 mg orally once daily

Safety

Monitor for arrhythmias, infections, bleeding, and cytopenias

Drug Interactions

- Strong CYP3A inhibitors: Avoid concomitant use; if unavoidable, reduce dose
- Strong/moderate CYP3A inducers: Avoid concomitant use; if unavoidable, increase dose

CAR T-Cell Therapy: Administration and Safety of Lisocabtagene Maraleucel (Liso-cel)[16,17]

Liso-cel is approved for R/R CLL/SLL after ≥2 prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor.

Administration

- 3 days of lymphodepleting chemotherapy with 30 mg/m^2 daily IV fludarabine and 200 mg/m^2 daily IV cyclophosphamide
- Patients are then infused with IV liso-cel 2-7 days after lymphodepletion

Premedication

- 650 mg acetaminophen and 25-50 mg IV or oral diphenhydramine (or another H1-antihistamine) 30-60 min before liso-cel infusion
- Possible prophylaxis:
  - Cytopenias: G-CSF
  - Infections: IVIG, vaccinations, other antiviral and antifungal prophylaxis

Acute Toxicities

- Cytokine release syndrome (CRS)
- Immune effector cell–associated neurotoxicity syndrome (ICANS)
- Cytopenias
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome

Delayed Toxicities

- B-cell aplasia/hypogammaglobulinemia
- Prolonged cytopenias
- Late infections
- Long-term neurologic events/movement and neurocognitive treatment-emergent AEs
- Transient cardiac toxicities
- Secondary malignancies

Monitoring

- Monitor patients for at least 1 wk after infusion for CRS and neurologic toxicities (eg, ICANS) or until resolution of those toxicities
- Patients should remain within 2 hr of treatment center for at least 2 wk and avoid driving for at least 2 wk
- Monitor for delayed toxicities

AF, atrial fibrillation; BCL2i, BCL2 inhibitor; BTKi, BTK inhibitor; cBTKi, covalent BTK inhibitor; CLL, chronic lymphocytic leukemia; CIT, chemoimmunotherapy; G-CSF, granulocyte colony-stimulating factor; HCT, hematopoietic cell transplantation; IR, immediate release; LN, lymph node; mAb, monoclonal antibody; MRD, measurable residual disease; ncBTKi, noncovalent BTK inhibitor; PFS, progression-free survival; PPI, proton pump inhibitor; SLL, small lymphocytic lymphoma; TLS, tumor lysis syndrome.

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