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Case-Based Discussion

Health Plan Best Practice

Chronic lymphocytic leukemia (CLL) is a chronic lymphoproliferative disorder (lymphoid neoplasm). It is characterized by a progressive accumulation of functionally incompetent B lymphocytes, which are usually monoclonal in origin.

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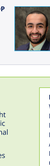

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CASE INITIAL PRESENTATION

A 65-year-old male presented to his PCP with complaints of fatigue and drenching night sweats. Bone marrow aspiration and biopsy revealed hypocellular marrow with chronic lymphocytic leukemia involving 80-90% of marrow. Flow cytometry revealed monoclonal B-population, CD5 positive, 60% of total cells.

PMH: patient takes OTC proton pump inhibitors a few times a week, tension headaches
PE: Enlarged mobile lymph nodes bilaterally (~1.5 cm), no palpable spleen or liver.

Laboratory findings
WBC: 102 X 109/L
Lymphocytes: 79 X 109/L
Hb: 10.4 g/dL
Platelets: 180 X 109/L
ANC: 1,900/mm3
LDH: 1470 U/L
Cytogenetics: del(11q), IgVH-unmutated
beta2M: 3.0 mg/L
Rai Stage III

TREATMENT PLAN

Additional tests are not essential to diagnose CLL but may help predict the prognosis or assess the tumor burden and are recommended before starting treatment. Baseline evaluation of patients with CLL should include molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes, *TP53* mutation and IGHV mutational status, beta-2-microglobulin, and CpG-stimulated metaphase karyotype for complex karyotype (CK).[1,2]

In general practice, patients with asymptomatic early-stage disease (Rai Low 0, Binet A), should be monitored without therapy unless they have evidence of disease progression, threatened end organ function, or significant disease-related symptoms. Patients with intermediate-risk (Rai stages I and II) and high-risk (Rai stages III and IV) disease usually benefit from the initiation of treatment.

Asymptomatic early-stage CLL

Regardless of risk factors, the standard of care is observation ("watch and wait") rather than immediate treatment

Symptomatic early-stage CLL or advanced-stage CLL

- Tumor characteristics: cytogenetics and molecular genetics for mutation identification
- Patient characteristics: fit or unfit status
- Duration of treatment: continuous vs. fixed duration
- Goals of ameliorating symptoms, improving progression-free and overall survival and reversing cytopenias

Current Recommended Treatments in CLL

The National Comprehensive Cancer Network (NCCN) designates Bruton's tyrosine kinase inhibitors (BTKi), acalabrutinib (preferred), zanubrutinib (preferred), or ibrutinib (other recommended regimen), with or without obinutuzumab as category 1 front-line treatment options for CLL.[2]

Mechanism of action	BTK inhibitor			BCL-2 inhibitor	Anti-CD20 monoclonal antibody	
Drug	Ibrutinib	Acalabrutinib	Zanubrutinib	Venetoclax	Obinutuzumab	Rituximab

Another preferred front-line option is the use of the BCL-2 inhibitor venetoclax in combination with the anti-CD20 monoclonal antibody, obinutuzumab. This represents a notable shift away from traditional cytotoxic-based chemotherapy toward oral targeted therapy-based regimens as the preferred treatment strategy.

The guidelines also outline various alternative regimens for situations where the disease proves refractory or recurs following front-line treatment.

The goals of treatment for patients with CLL are to:

- alleviate constitutional symptoms
- improve cytopenias
- alleviate bothersome splenomegaly and liver lymphadenopathy

The choice of CLL therapy is based on patient and tumor characteristics and goals of therapy

There is no agreed upon standard front-line treatment regimen in CLL and clinical practice varies, therefore treatment pathways and coverage policies should support access to various treatment options.[3]

CASE EIGHT-MONTH FOLLOW-UP

The patient was started on ibrutinib based on need for treatment and high-risk features of deletion 11q as well as an IgVH-unmutated status. The patient returned to the clinic for a follow-up appointment 8 months after starting ibrutinib. Clinical assessment demonstrated partial remission, but he is complaining of joint pain and recent episodes of lightheadedness and an EKG shows he has developed atrial fibrillation.

Intolerance to Treatment

It is not uncommon for CLL patients to switch treatments during their journey with the disease. The patient has demonstrated partial response to BTKi treatment, so switching to a second generation BTKi and referral to cardiology is a reasonable approach.

BTK inhibitors have common side effects, including bleeding, hypertension, atrial fibrillation, joint pain, potential skin rash, and diarrhea. Many patients report fatigue, arthralgias or myalgias, and headaches.[4] Second-generation BTK inhibitors have a more favorable toxicity profile, not only in terms of cardiovascular effects but also in other aspects, such as diarrhea, muscle pain, and joint pain. Acalabrutinib and zanubrutinib were compared to ibrutinib in the ELEVATE-RR trial (acalabrutinib vs. ibrutinib) and the ALPINE study (zanubrutinib vs. ibrutinib).[5,6] Both trials focused on patients with relapsed or refractory CLL and demonstrated that the second-generation BTK inhibitors had significantly fewer side effects compared to ibrutinib.

An indirect cross-trial comparison of acalabrutinib versus zanubrutinib indicated that the risk of experiencing grade 3 or more severe adverse events, such as atrial fibrillation, hemorrhage, or events leading to treatment discontinuation, was similar for acalabrutinib and zanubrutinib.[7] Nevertheless, acalabrutinib and zanubrutinib have not been directly compared in a head-to-head fashion.

Suggested Treatment Algorithm in Patients Intolerant of 1st Generation BTK Inhibitor

1st generation BTKi intolerance

- Manage Side Effects
- Switch to another covalent BTK inhibitor → 2nd generation BTKi
- Abandon Covalent BTK inhibitor → • Clinical trial participation • Rituximab-based combinations • Venetoclax

1st generation BTKi: ibrutinib
2nd generation BTKi: acalabrutinib, zanubrutinib

Treatment toxicities are an essential consideration in the selection and switching of BTK inhibitors

Approaches to address side effects include supportive care or dose reductions, switching to an alternative covalent BTK inhibitor, or abandoning covalent BTK inhibitors for alternative forms of treatment.[3]

CASE ADHERENCE AND PATIENT QUALITY OF LIFE (QoL)

The patient was referred to a cardiologist for a-fib management and switched to the second generation BTKi zanubrutinib. The patient asks about the dosing of zanubrutinib because he does not want to have to go into the hospital for his CLL treatment and prefers to have a medication he can take at home.

Medication Adherence

Patients have the right to make informed decisions about their healthcare. Understanding their treatment preferences allows healthcare providers to tailor treatment plans that align with the patient's values, goals, and preferences. This helps ensure that the patient is an active participant in their care and can make choices that best suit their needs. Questions to ask the patient to promote shared decision making around their CLL treatment may include:

- **What are their treatment preferences?**
- **Do they want time-limited vs continuous therapy?**
- **Do they want all oral vs IV plus oral therapy?**

Patient, treatment, and health system factors, such as older age, increased medication and comorbidity burden, previous cancer therapy, health insurance type, and higher outpatient visits, have been identified as factors influencing adherence to oral therapies for CLL.[8] Optimal selection of frontline therapy from multiple effective options may be a challenge for clinicians, who need to consider both disease and patient factors in conjunction with a view to sequencing available therapies in event of disease relapse.

Factors influencing adherence to oral therapies for CLL:[8]

- **Health System Factors** — Health insurance type
- **Treatment Factors** — Medication burden
- **Patient Factors** — Older age, geography

The BCL-2 inhibitor, venetoclax, has offered patients an alternative to BTKis as a fixed-duration treatment providing durable responses. Further, in those patients progressing or intolerant to BTKis, venetoclax-based therapy remains highly efficacious. Both BTKis and venetoclax are oral self-administered therapies that may offer convenience for patients. It is important to consider the differences in longer-term adherence and discontinuation since BTKis are to be taken daily unless the patient experiences an adverse event or disease progression, while venetoclax is a fixed-duration treatment given for 12 months as frontline therapy in combination with obinutuzumab. Given the importance of sustained adherence for disease control in CLL, dosing frequency may be an important consideration for patients and physicians.

Treatment adherence and impact on QoL are key factors when developing coverage policies

High medication adherence is needed to achieve optimal outcomes in CLL.[3]

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This Market Insights program was supported by BeiGene.