CRA Insights

Life Sciences

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When Innovation Outpaces Access: Closing the Gap in CLL Care

Summary: Chronic lymphocytic leukemia (CLL) treatment has improved markedly over recent years – moving away from systemic chemotherapy to newer targeted oral therapies, improving patient quality of life, and increasing five-year survival rates to nearly 90%.[1] But while the innovation landscape continues to advance, inconsistent adherence to clinical guidelines, the failure to evaluate all patient risk factors, and obstructive insurance coverage can limit patients' ability to access and benefit from innovative treatments.

In advance of Blood Cancer Awareness Month, CRA, BeOne Medicines, and key partners will release their assessment of key pressure points across the care pathway, culminating in a **first-of-its-kind report examining the CLL healthcare ecosystem and the systemic challenges that limit patients' access to care**, including biomarker testing delays, inconsistent adherence to clinical guidelines, insurance barriers, and other major barriers. This report synthesizes perspectives from the broader blood cancer community to advance more patient-centered approaches to CLL care. Only when systemic access barriers are eliminated can patients fully benefit from innovative medicines designed to improve long-term outcomes.

Chronic lymphocytic leukemia (CLL) is primarily a disease of older adults, with a median age at diagnosis of approximately 70–72 years.[2] Patients can have multiple comorbidities, including cardiovascular disease, hypertension, renal impairment, and other chronic conditions, at the time of diagnosis that can complicate treatment selection and tolerability.[3] CLL is not the same in every patient, with outcomes influenced by genetic risk factors such as TP53 mutations and IGHV status.[4] Many patients are initially managed under a "watch-and-wait" approach before requiring therapy, adding further complexity.[5] Together, these factors make individualized, guideline-directed treatment essential to improving patient outcomes.

Prior to 2010, CLL treatment relied on chemotherapy, but recent innovation has shifted the paradigm. Chemotherapy caused serious side effects for patients and produced lower efficacy relative to today's targeted treatments.[6] In the 2010s, the standard of care evolved to early immunotherapies, often used in combination with chemotherapy.[7] While these therapies improved survival, side effects (e.g., fatigue and immunosuppression) were profound and left patients vulnerable to dangerous infections.[8] There were few biomarker or risk-targeted options, especially if patients had comorbidities.[9] Median progression-free survival (PFS) was four to five years, and only two to three years for high-risk patients.[10]

New, more efficacious CLL treatments compared to chemotherapy were introduced with the FDA approval of oral treatments: the first Bruton's tyrosine kinase inhibitor (BTKi) in 2014 and the first B-cell lymphoma 2 inhibitor (BCL2i) in 2016. These targeted therapies specifically identify cancer cells while minimizing damage to healthy cells.[11] There is evidence that:

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- **Continuous CLL therapy has been shown to improve long-term patient outcomes.** First-generation BTKis extended PFS by 7.6 years compared to chemotherapy alone.[12] Second-generation BTKis built on these survival gains and improved selectivity and tolerability. As such, second-generation BTKis are more precise and may cause fewer side effects by avoiding unintended targets, increasing three-year PFS in relapsed/refractory CLL from 54 percent to 66 percent compared to a first-generation BTKi.[13] Some next-generation treatments have demonstrated exceptional long-term survival benefits over chemoimmunotherapy, increasing 78-month PFS from 31 percent to 72 percent compared to chemoimmunotherapy alone.[14]
- **Fixed-duration CLL treatments may enable time off therapy or fewer doctor visits.** Fixed-duration treatments offer the promise of treatment-free intervals for some patients, depending on the specific characteristics of their disease.[15] Emerging fixed-duration treatments have the potential to shift the treatment paradigm in the future but only if fixed-duration therapies elicit a more durable response, demonstrate sustained PFS, carry a reduced infection risk compared to continuous BTKi therapy, and are more convenient to administer; current fixed-duration options do not achieve all of these goals.[16]

Innovation in CLL allows clinicians to tailor treatment based on a patient's unique risk factors. CLL is often detected through routine blood tests[17] and treatment is initiated after symptoms develop.[18] Clinicians should ideally select the most appropriate therapy based on a patient's unique risk factors and treatment goals, including:[19]

- Genetic risk (e.g., Del(17p), TP53, and IGHV mutations) assessed through biomarker testing[20]
- Comorbidities (e.g., cardiovascular disorders, hypertension, bleeding risk, liver function, and kidney impairment)
- Age factors (median age of CLL diagnosis is 72; patients over 70 often present with more advanced disease)
- Current medications (e.g., warfarin, nephrotoxic drugs, and CYP3A inhibitors)[21]
- Patient preference (e.g., type of treatment [oral vs. intravenous], survival outlook, types and risk of side effects) and treatment goals[22]

Updated treatment pathways recommend targeted therapies over chemotherapy. CLL clinical guidelines recommend that patients begin with continuous covalent BTKi therapy or fixed-duration BCL2i therapy based on biomarker tests, patient preference for therapy duration, and patient comorbidities. If the first- or second-line treatment does not work, a patient may try an alternative combination of BTKis, BCL2is, and anti-CD20 antibodies; other options may include chimeric antigen receptor T-cell (CAR-T) therapy, or stem cell transplantation.[23] Guidelines may change to reflect treatments for CLL in development, including BTK degraders, second-generation BCL2is, and bispecific monoclonal antibodies that could help patients with relapsed/refractory CLL.[24]

Due to access barriers and non-adherence to clinical guidelines, **not all CLL patients have access to treatments that may give them the greatest opportunity for survival and the best quality of life.**[25] Many patients are not tested to understand their genetic risk factors even though many patients are high risk; clinical data now show newer medicines have meaningfully improved long-term outcomes for high-risk patients.[26] Clinical guidelines are not always consistently followed, and some patients may be initiated on chemotherapy instead of targeted oral therapies.[27] This could be due to site of service inequities where large hospitals have greater access and familiarity with the latest treatment options and biomarker testing compared to smaller providers or rural treatment centers.[28] Insurance coverage may lag behind clinical guidelines with utilization management (UM) practices like step therapy requiring patients to fail on less efficacious therapies before accessing the one prescribed by their doctor.[29] UM practices

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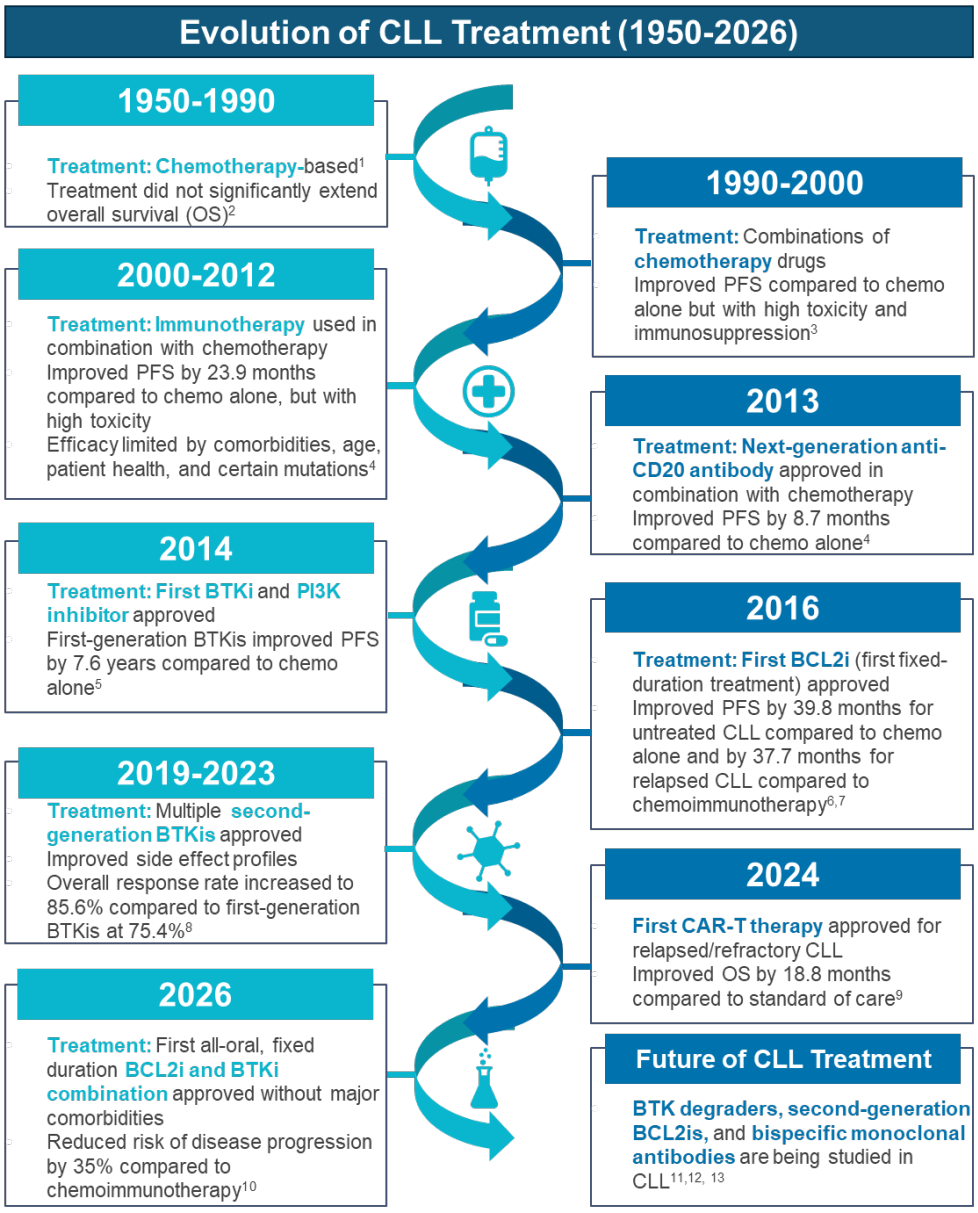
limit clinician flexibility to select the best treatments based on patients' unique medical needs, often **delaying or denying CLL patients getting the right treatment at the right time.**[30]

What's next? This analysis offers an initial perspective on the gap between innovation and access in CLL care. Additional insights will be shared in the coming weeks that further explore key challenges and efforts to close this gap.



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