CLL: Is continuous therapy a thing of the past?

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Chronic lymphocytic leukemia (CLL) remains a challenging disease, with a significant proportion of patients requiring continuous therapy. For years, chemoimmunotherapy regimens like fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine and rituximab (BR) served as the backbone for fit patients, but these come with considerable toxicity and no defined treatment cessation.

The advent of targeted therapies has reshaped the treatment guidelines, offering chemotherapy-free options. The question for clinicians now is not just efficacy, but also the duration of therapy and its impact on patient quality of life.

KEY TAKEAWAYS

- The Pivot: Fixed-duration venetoclax combinations provide a time-limited, chemotherapy-free treatment option for fit patients with untreated CLL, moving away from continuous therapy.
- The Data: This approach aims for deep and durable responses, allowing patients a break from active treatment.
- The Action: Clinicians should consider fixed-duration venetoclax regimens for appropriate fit patients, balancing efficacy with the benefit of treatment-free intervals.

Chronic lymphocytic leukemia is characterized by the accumulation of mature but functionally incompetent lymphocytes, primarily B cells, in the blood, bone marrow, and lymphoid organs. The disease course is highly variable, ranging from indolent forms requiring no immediate intervention to aggressive presentations necessitating prompt treatment. Historically, the goal of therapy in CLL has been to achieve maximum response and prolong survival, often through continuous treatment. The toxicity profile of traditional chemoimmunotherapy, particularly in older or less fit patients, has long driven the search for more tolerable and effective alternatives.

The unmet need in CLL has centered on improving response depth and duration, reducing treatment-related toxicities, and, most importantly, offering patients a finite treatment period, which is a major stake for patient quality of life. Continuous therapy, while effective, can lead to cumulative toxicities, patient fatigue, and a constant burden of medical appointments and drug administration. The desire for treatment-free intervals, allowing patients to live without daily medication and its associated side effects, has become a significant driver in drug development. This is particularly relevant for younger, fitter patients who may face many years of disease management.

The evolution of CLL treatment

For many years, FCR was considered the standard of care for fit patients with untreated CLL, demonstrating superior progression-free survival and overall survival compared to other chemoimmunotherapy regimens. But FCR is associated with significant myelosuppression, infectious complications, and secondary malignancies, particularly in older patients.

BR offered a less intensive alternative for patients who could not tolerate FCR, but still carried considerable toxicity. The choice between these regimens often hinged on patient fitness, age, and specific cytogenetic risk factors, such as the presence of TP53 deletion or mutation, which predict poor response to chemotherapy.

The introduction of targeted therapies, specifically Bruton's tyrosine kinase (BTK) inhibitors and BCL-2 inhibitors, marked a significant shift. BTK inhibitors, like ibrutinib, acalabrutinib, and zanubrutinib, offer continuous, chemotherapy-free treatment, demonstrating superior efficacy over chemoimmunotherapy in many settings. But these are indefinite therapies, meaning patients remain on treatment until progression or unacceptable toxicity. This continuous exposure can lead to cumulative side effects, including cardiac events, hypertension, and bleeding, which, while manageable, impact long-term quality of life. For a deeper dive into these options, consider our coverage on BTK inhibitors vs. venetoclax combinations in CLL.

Venetoclax, a BCL-2 inhibitor, works by restoring apoptosis in CLL cells. Its approval, initially for relapsed/refractory CLL and later for first-line use, introduced the concept of fixed-duration therapy. This approach aims to achieve deep remissions, including undetectable minimal residual disease (MRD), allowing patients to stop treatment after a defined period. The promise of a treatment-free interval is a powerful motivator for both patients and clinicians, offering a return to a semblance of normalcy without the constant reminder of chronic disease management. The Oxford Handbook of Clinical Haematology provides a concise reference for these evolving treatment paradigms.

Understanding fixed-duration venetoclax

Fixed-duration venetoclax regimens typically involve combination therapy, often with an anti-CD20 monoclonal antibody like obinutuzumab or rituximab. The rationale for combination is to achieve deeper and more rapid responses, thereby increasing the likelihood of achieving undetectable MRD, which is a strong predictor of prolonged progression-free survival. The duration of venetoclax treatment is usually 12 to 24 months, depending on the specific regimen and patient characteristics. This contrasts sharply with the indefinite treatment duration of BTK inhibitors, offering a distinct advantage for patients seeking a finite treatment course.

The CRISTALLO trial, a phase 3 study, evaluated fixed-duration venetoclax plus obinutuzumab (VenO) against standard chemoimmunotherapy (FCR or BR) in fit patients with previously untreated CLL. The trial aimed to determine if VenO could provide superior efficacy while offering the benefit of a fixed treatment duration. Patients were randomized to receive either VenO for a defined period or FCR/BR according to physician choice and local guidelines. The primary endpoint focused on progression-free survival, with secondary endpoints including overall survival, rates of undetectable MRD, and safety profiles. The design sought to directly compare the newer, chemotherapy-free approach with established standards.

The trial's primary analysis sought to establish whether the fixed-duration VenO regimen could improve outcomes compared to traditional chemoimmunotherapy. The expectation was that VenO would offer at least non-inferior efficacy, coupled with a more favorable toxicity profile and the significant advantage of a treatment-free interval. The ability to achieve deep remissions, particularly undetectable MRD in the bone marrow and peripheral blood, is a key metric for fixed-duration therapies, as it correlates with longer remission durations. The CRISTALLO trial's findings would directly inform clinical practice regarding first-line treatment choices for fit CLL patients.

Clinical implications and patient considerations

The shift towards fixed-duration therapies like VenO represents a significant advancement for patients with CLL. For fit patients, the prospect of achieving a deep remission and then stopping treatment for a period can profoundly impact their quality of life. This allows for a return to normal activities without the constant burden of medication, clinic visits, and the psychological impact of continuous cancer treatment. The CRISTALLO trial's results, by comparing VenO directly with FCR/BR, provide important data to guide these treatment decisions, which is a major stake for patient outcomes. Our previous coverage on fixed-duration BCL-2 combinations further explores this concept.

But the choice of therapy is not solely about efficacy; it also involves managing potential toxicities. While chemoimmunotherapy carries risks of myelosuppression and infection, venetoclax is associated with tumor lysis syndrome (TLS), particularly during the ramp-up phase. Careful monitoring and prophylaxis are essential to mitigate this risk. Other common side effects include diarrhea, nausea, and neutropenia. Clinicians must weigh these different toxicity profiles when discussing treatment options with patients, ensuring they understand the potential benefits and risks of each approach. The goal is to select a regimen that maximizes efficacy while minimizing adverse events and supporting patient preferences.

The long-term implications of fixed-duration venetoclax regimens are still being elucidated. While patients enjoy treatment-free intervals, the question of when and how to re-treat upon progression remains. The CRISTALLO trial's follow-up data will be critical in understanding the durability of responses and the efficacy of subsequent therapies. This ongoing research will help define optimal sequencing strategies for patients who eventually relapse after fixed-duration treatment. The evolving market of CLL therapy means that clinicians must stay abreast of new data to provide the best possible care, a topic we have explored in aligning patient priorities with targeted therapy.

The CRISTALLO trial's primary analysis provides important insights into the role of fixed-duration venetoclax in untreated CLL. It offers a compelling alternative to traditional chemoimmunotherapy, particularly for patients who prioritize a finite treatment course. The data will likely reinforce the trend towards chemotherapy-free regimens in CLL, further solidifying the place of targeted therapies in the first-line setting. But the nuances of patient selection, toxicity management, and long-term follow-up remain critical considerations for clinical practice. The next step involves integrating these findings into updated treatment guidelines and ensuring equitable access to these innovative therapies.

CLINICAL IMPLICATIONS

The CRISTALLO trial's primary analysis on fixed-duration venetoclax versus chemoimmunotherapy in fit, untreated CLL patients confirms a clear direction for the field. Clinicians now have robust evidence to support moving away from the toxicities of FCR or BR for many patients. The ability to offer a time-limited treatment, with the promise of a treatment-free interval, is a significant quality-of-life improvement that cannot be overstated.

But this does not mean a one-size-fits-all approach. While fixed-duration venetoclax offers compelling advantages, the choice between it and continuous BTK inhibitor therapy will depend on individual patient characteristics, comorbidities, and preferences. Some patients may prefer the convenience of a daily oral pill over the initial intensive ramp-up and monitoring required for venetoclax, despite the indefinite duration. Others will prioritize the chance to stop treatment entirely.

The industry will continue to push for deeper, more durable responses, and the competition between fixed-duration and continuous targeted therapies will drive further innovation. The focus will likely shift to

> identifying which patients benefit most from each approach, perhaps through more refined biomarker analysis. For now, the CRISTALLO data provides a strong argument for fixed-duration venetoclax as a preferred first-line option for many fit patients.

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