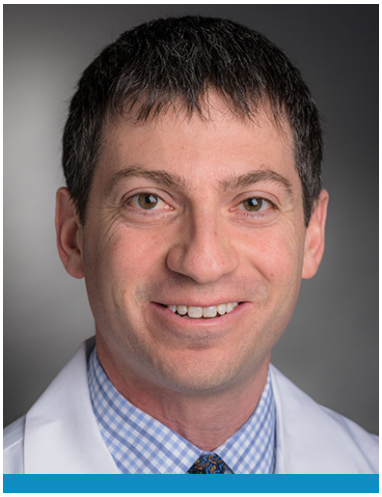
Managing Chronic Lymphocytic Leukemia as a Chronic Disease: A Q&A With Matthew S. Davids, MD



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***AJMC®*: What are your general impressions of the chronic lymphocytic leukemia (CLL) treatment landscape and how you've seen it evolve over the last couple of years?**

DAVIDS: We have had effective treatments for CLL for quite some time now, which first started with chemotherapy and then the addition of immunotherapy with rituximab in the 2000s. The approach of combination chemoimmunotherapy was good at putting the disease into remission for most patients for a period, but inevitably, the disease would return. What we found is that chemoimmunotherapy was not as effective with repeated use, and patients would commonly die from either infectious complications or progression of the CLL itself.

Over the last 5 years, there has been a revolution in how we approach the treatment of this disease, with 5 new targeted therapies specifically approved for CLL. This started with the new anti-CD20 obinutuzumab antibody back in 2013, which is more potent than rituximab in killing CLL cells. We now have longer-term evidence that there is an overall survival benefit to starting with obinutuzumab plus chlorambucil instead of rituximab plus chlorambucil for initial therapy in older patients. Following the approval of obinutuzumab, there were approvals of several mechanistically diverse small molecule, targeted oral agents, including ibrutinib and idelalisib in 2014 and then venetoclax in 2016. The most recent approval was duvelisib in 2018.

With so many effective tools in our therapeutic armamentarium, the challenge now is in deciding when to use single-agent therapy and when to use a combination approach. For combination approaches, an additional challenge is how we put these agents together in the most rational way: the most effective, the best tolerated, and the most cost-efficient.

***AJMC®*: Given the treatments available right now, how has your perspective changed, and how important is it to think of CLL as a chronic disease as opposed to treating to a goal of remission?**

DAVIDS: One interesting development in the last couple [of] years is that we have seen long-term data published from the original chemoimmunotherapy studies of the fludarabine plus cyclophosphamide plus rituximab [FCR] regimen, and we now know that there is a subset of CLL patients who may be cured just from the chemotherapy alone. That has influenced how we approach frontline treatment, and we have young, fit patients with mutated *IGHV* where FCR has been still considered the gold-standard initial therapy. At the recent American Society of Hematology Annual Meeting, we saw the initial data from a large, randomized phase III study of FCR versus ibrutinib plus rituximab for frontline treatment of younger patients with CLL. This study showed a progression-free and overall survival benefit for the ibrutinib plus rituximab arm, though the benefits were mainly seen [in] patients with unmutated *IGHV*. For patients with mutated *IGHV*, it remains uncertain which regimen is best to start with, and discussions with such patients need to be individualized.

Different types of patients with CLL may benefit from different therapeutic approaches. In younger, fit patients, it might make sense to use a multidrug combination and try to achieve long-term remission with time-limited

therapy. However, the average age of CLL diagnosis is 72, and most patients do not need treatment for a few years. So, for your average patient needing initial treatment in their late 70s, it might make more sense to use a sequential single-agent type of approach and to try to convert CLL truly into a chronic disease and treat it with continuous therapies, in the way you would treat hypertension. A challenge there, though, is that these new targeted therapies are orders of magnitude more expensive than antihypertensives, so a sequential, continuous administration, novel-agent–based approach in CLL is costly. This model may work better than aggressive combination approaches for [that large group of] older, frailer patients with lower-risk CLL.

***AJMC®*: What are some of the most important factors, in your experience, when determining those treatment options for patients with CLL?**

DAVIDS: The most important factor that we know of right now is the mutational status of *TP53*. When it is mutated or deleted, which is also known as del(17p), the patient will not respond well to chemoimmunotherapy. If they have either *TP53* mutation or del(17p), they should not be getting chemotherapy-based approaches. This applies to a small percentage of patients, about 10% at diagnosis, and currently, the only approved frontline option for these patients is ibrutinib. However, this may also be changing, with the recent results from the phase 3 CLL14 study, which is evaluating venetoclax with obinutuzumab compared with chlorambucil with obinutuzumab. Although the results of this study have not yet been published, it is a registrational study that could lead to a frontline label for venetoclax, a drug which is very active for patients with *TP53*-dysfunctional CLL. Another promising approach now being studied is a combination of venetoclax with a Bruton tyrosine kinase [BTK] inhibitor, with or without obinutuzumab.

Outside the *TP53* setting, several other patient characteristics should be considered. One is the *IGHV* test. If *IGHV* is mutated, patients can still be considered candidates for chemoimmunotherapy, though initial therapy with ibrutinib is also now an option. Patients with unmutated *IGHV* should generally be getting ibrutinib as their first treatment, but that may be evolving soon, as other novel agents, such as venetoclax, move into the frontline setting.

Many other factors come into play when deciding on frontline therapy, including age, specific medical comorbidities, and patient preferences. The chemotherapy regimens are given, for the most part, intravenously, and [they] are designed as time-limited therapies, whereas when given as single agents, the oral drugs are continuously given for the long term. Many patients are candidates for both continuous single-agent [and] time-limited combination approaches. This often results in a long conversation with their hematologist over which approach may be best for an individual patient. Although these new novel drugs are often well tolerated, I do still have patients who opt for chemotherapy-based approaches because they want 6 months of time-limited treatment with the possibility of going into remission for a few years. Other patients are worried about the toxicities of chemotherapy and would prefer to avoid it by going onto a novel drug even if it means they must be on it for many years.

***AJMC®*: Can you talk a bit about some challenges presented by the increasing number of available targeted agents?**

DAVIDS: One challenge that comes to mind, particularly for general oncologists and hematologists in practice, is that we have 5 new drugs [that were] FDA approved for CLL in the last few years. There are similar numbers of new approvals in several other types of cancers, so I could imagine it is quite challenging to keep up with all the nuances of prescribing these drugs. Each of these oral agents has a unique adverse event profile. For example, venetoclax is so potent that it can cause tumor lysis syndrome [TLS], even though it's an oral agent being used in a chronic disease. The manufacturer has developed an effective TLS mitigation plan, but prescribers need to be familiar with this plan to be able to start the drug safely.

Another factor that certainly comes into play is the cost of these drugs. The targeted therapies for CLL generally cost more than $100,000 per year. Particularly for our Medicare patients, we have found these costs to be challenging, because we can't access the company-based assistance programs. In these situations, we have been relying on foundation support, which is hugely helpful, but sometimes patients may not qualify, or at certain times of year, the programs might not be sufficiently funded. For patients who don't have great supplemental prescription drug coverage, co-pays can sometimes be cost prohibitive. With the cost of single-agent novel therapy being so high, it may be challenging to pay for combination regimens of novel agents. For example, a popular combination in trials now is ibrutinib and venetoclax given together, which would cost [more than] $200,000 a year.

The way that we are trying to contain costs of these combination novel-agent regimens is with time-limited therapy. Maybe a year of both drugs costs $200,000, but you get 7 years of remission without the need for ongoing therapy, as opposed to using ibrutinib alone as a continuous therapy for 7 years, which would cost more than $700,000.

If these combinations are effective enough, it may actually be a cost savings, provided that the remissions are durable. If not, they may be quite a bit more expensive, in which case we would probably stick with a sequential novel-agent monotherapy approach for most patients.

***AJMC®*: What has been your experience regarding reimbursement for targeted therapies?**

DAVIDS: Overall, it has been a pretty positive experience so far. The situations in which I have encountered denials are typically when I am trying to use a drug off-label. For example, there are now data suggesting that a new BTK inhibitor, acalabrutinib, may be better tolerated than ibrutinib for some patients. Although [it's] approved in mantle cell lymphoma, acalabrutinib does not yet have a label in CLL, so I have received some pushback from payers on off-label use of acalabrutinib in CLL.

***AJMC®*: Considering how much the targeted therapy landscape for CLL has expanded over the past several years, how do you see this spectrum continuing to develop? What are some of the opportunities and challenges you see as that future unfolds?**

DAVIDS: In the near future, results from the CLL14 study may shift the treatment spectrum again, as it is a potentially label-enabling study for venetoclax in the frontline setting. That would be a significant development, because unlike ibrutinib, this was designed as a time-limited therapy. There are also ongoing studies combining novel agents with chemoimmunotherapy, such as a study we are leading of ibrutinib in combination with FCR for younger, fit CLL patients. Preliminary results with this approach are also promising to enhance the curative potential of FCR in that population.

The other thing on the horizon, a little further out, is chimeric antigen receptor [CAR] T-cell therapy in CLL. CAR-T has been slower to develop in CLL as compared with acute lymphoblastic leukemia or diffuse large B-cell lymphoma, the 2 indications where they are now approved. However, there is an evolving data set from multiple different companies on CAR-T in CLL [that] looks promising. So CAR-T is probably headed toward an approval in CLL, and it may become an important option, particularly for high-risk CLL patients who have progressed on novel-agent–based therapies.

The other interesting development is that we have new molecules coming along [that] hit the same targets as the original drugs but may do so more effectively or with less toxicity. I mentioned acalabrutinib previously, but there is another BTK inhibitor in late-stage development, zanubrutinib. There is a known resistance mechanism of ibrutinib already identified, and there are a couple of new BTK inhibitors in the clinic now that, at least in vitro, target that resistance mutation effectively, which is an exciting development. There is also a newer PI3K inhibitor drug called umbralisib.

This new wave of drugs has the potential to be better tolerated and/or more effective than the existing agents. This will, hopefully, put some competitive pressure on manufacturers of existing agents and possibly help with pricing in the coming years as these new agents get approved. Nevertheless, as we have seen in other diseases, the arrival of newer agents may not drive prices down as much as we hope, and it is worth noting that all these drugs are far from being generics at this point. Therefore, it is going to remain a challenge in terms of how we pay for all these great new drugs. Providers and institutions will need to continue to work with the insurance companies to try to figure out how to most efficiently deliver these drugs to our patients.