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Personalizing First-Line Therapy for CLL

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Dr. Wierda:
Hello, and welcome. Today we're talking about first-line therapy for patients with chronic lymphocytic leukemia, or CLL.

This is a continuing education program on ReachMD, and I'm William Wierda from MD Anderson in Houston, Texas.

Dr. Davids:
And I'm Dr. Matthew Davids from Dana-Farber Cancer Institute in Boston, Massachusetts.

Dr. Wierda:
Let's start, Matt, with reviewing biomarkers for patients with CLL. How do you test for biomarkers in newly diagnosed patients and patients who are going on first-line therapy?

Dr. Davids:
So the thing with biomarkers in CLL is that they can generally be sent from the blood. You don't need to do a bone marrow biopsy test. So after you've confirmed the diagnosis with flow cytometry, there's kind of 3 or 4 main markers you want to send, which include the FISH test to look at cytogenetics but also a CpG-stimulated karyotype if you have access to that in your lab. Secondly, the IGHV mutational status. And then third, you want to do actual sequencing for the TP53 mutations.

And so this is a distinction from FISH, which looks for deletion 17P, so it’s important to actually do both of these. Certainly, if you’re still considering chemoimmunotherapy, you want to avoid that in patients with TP53 aberration, whether deletion or mutation. But increasingly, we're really not using chemoimmunotherapy in the treatment of CLL. And even there, there's some distinctions being made that we'll talk about between patients who have TP53 aberration or not with respect to which of the targeted therapies we might recommend.

I'll also emphasize that IGHV mutational status can be helpful to check. It really identifies the biology of the disease and it doesn't change over time. So if you check it at diagnosis, you'll know that throughout the lifetime of the patient. It can influence the time to first treatment and also it can be helpful for counseling patients there.

And again, it's increasingly influencing our choice of targeted therapies in this disease.

Dr. Wierda:
Do you test these factors at initial diagnosis and when patients go on first-line therapy? Can you give us some perspective on that?

Dr. Davids:
Yeah. So I do test all of these factors at diagnosis to really understand the biology for that individual patient and help to counsel them about sort of their likely course and time to first treatment. Importantly, the IGHV test does not change, so I do not retest that at the time of initial treatment. But if I have a patient who's gone several years on a watch-and-wait approach and they're starting treatment, I will retest the FISH and the TP53 mutation to see if that's changed. Sometimes you can see clonal evolution, even in the absence of treatment, so it's helpful to know that going into frontline therapy.

Dr. Wierda:
And my perspective is how we think about these factors and patients' expectations for outcomes will be different if we're talking about first-line therapy with continuous BTK inhibitor-based therapy versus fixed-duration or time-limited therapy. So we'll talk a little bit more about that as we go through our discussion.

Dr. Davids:
So our second topic is really that we have a couple of great options now for first-line therapy for patients with CLL, and these include both time-limited treatments as well as continuous treatments. So, Bill, maybe review with us the advantages and disadvantages of both.

Dr. Wierda:
So as you indicate, we have 2 strategies that we can take for our patients in terms of first-line therapy, continuous therapy or maintenance therapy versus time-limited or fixed-duration therapy. And those 2 strategies will be driven by the agents that we use to treat the patients. And they have different aspects and components to them that are helpful in terms of us selecting which strategy to take.

And we'll start with continuous therapy. This is BTK inhibitor-based therapy. There are 3 covalent BTK inhibitors that we have available: ibrutinib, zanubrutinib, and acalabrutinib. There have been trials that have demonstrated a lower incidence of side effects and toxicities for the second-generation BTK inhibitors, being acalabrutinib and zanubrutinib. Those are agents that are easy to initiate. The requirements for monitoring initially are less intense than the fixed-duration treatment.

And so patients don't have to come back and forth to the clinic as much for initial monitoring, and it's a simple initiation process. They do have associated toxicities that we monitor for. Bleeding events, atrial fibrillation can occur, although it is an infrequent event. Hypertension as patients stay on these agents long term. In general, they're relatively well tolerated but do require patients to stay on them continuously.

And that's in contrast to time-limited or fixed-duration treatment. This is venetoclax-based therapy. The objective of this strategy is to get patients into a good, deep remission and off treatment in remission for a long period of time. Venetoclax, as I mentioned, is the agent that is the foundation of those regimens, and we have used venetoclax with CD20 antibody, venetoclax with BTK inhibitors and with CD20 antibody.

So there are toxicities associated with that require us to adjust our management. For example, the venetoclax initiation and ramp-up is a relatively intensive period where patients have to come back and forth to the clinic at least once a week for monitoring for the initial month to 2 months of initiation of that therapy.

Once patients are on the target dose of venetoclax, it's well tolerated and requires some monitoring, but less intense monitoring. Those regimens typically will include a CD20 antibody. There is associated infusion-related reactions that patients can experience with that, and there is some immune suppression that comes with the CD20 antibodies that require us to monitor for and be diligent about working up infection.

But I think in terms of that strategy being the time limited or fixed duration, it does afford patients a significant time off therapy. The other thing that we've been learning about fixed-duration targeted therapy is that patients generally will respond again when they're retreated

with those treatments. So you can expect to get a patient back in remission and off treatment again for their second-line therapy if you select time-limited therapy in that setting.

Dr. Davids:
Thanks, Bill. That was very comprehensive, and I don't have too much to add. I mean, I would just kind of emphasize that as we kind of think about these time-limited versus continuous options, other factors that are really critical include the patient's comorbidities. So when we have patients who have preexisting cardiovascular disease, if they've already been on anticoagulation, for example, it may push us away from continuous BTK inhibitor-based therapy. On the other hand, we sometimes have patients with significant renal dysfunction where we maybe are worried about tumor lysis syndrome. If they have bulky disease, that might push us away from venetoclax, potentially.

We also look, of course, at the genetics. And kind of going back to our initial discussion, if we have patients with TP53 aberration, I think a lot of us are still leaning toward the continuous BTK inhibitor-based approach to really prolong that initial PFS. But especially if we have patients with mutated IGHV, we're seeing particularly long remissions from, for example, venetoclax-obinutuzumab. We have a long-term follow-up now from the CLL14 study, about 6 years of follow-up, and the majority of those patients are still in remission if they have mutated IGHV 6 years after starting the venetoclax-obinutuzumab regimen.

We also have some exciting data that was published last year with doublet and triplet-based BTK/BCL2 combinations. Initially, a lot of that work was around ibrutinib plus venetoclax. Here in the US, we've been using more acalabrutinib and recently, we have the AMPLIFY study, which compared a doublet of acalabrutinib-venetoclax versus the triplet of acalabrutinib, venetoclax, and obinutuzumab to chemoimmunotherapy. And both those AV-containing arms had progression-free survival advantages over chemoimmunotherapy, were generally well tolerated with low cardiovascular risks. We did see some increase in infectious risk with the addition of the obinutuzumab in that study, but it’s great now to have these different options listed in the NCCN Guidelines and generally pretty available for patients.

Dr. Wierda:
For those of you just tuning in, you're listening to continuing education on ReachMD. I'm Dr. William Wierda, and here today with me is Dr. Matthew Davids. We're discussing first-line therapy for CLL.

Dr. Davids:
So you kind of touched on this already, Bill, but maybe just a little bit more detail now on some of the safety issues related to BTK inhibitors and BCL2 inhibitors around patient selection and sort of how you manage some of these toxicities.

Dr. Wierda:
Right, so in terms of selection of continuous therapy, and as you mentioned, atrial fibrillation is a risk, cardiac toxicity is a risk with even the second-generation BTK inhibitors, so we have to be careful about patients who have preexisting cardiac conditions if they're going on a maintenance therapy.

As you mentioned, anticoagulation can be a challenge if patients are going on the BTK inhibitors because they do act as agents that inhibit platelet aggregation and can be an increased risk for bleeding particularly in patients who are on anticoagulation.

In terms of the BCL2 inhibitor-based therapies, renal insufficiency can be a challenge and can exclude patients from treatment with the BCL2 inhibitor if their renal insufficiency is such that they're at significant risk for tumor lysis syndrome or complications with the BCL2 inhibitor-based therapy.

The BCL2 inhibitor-based therapy has been associated with neutropenia. So long term, we monitor for neutropenia. If it's early in treatment and I believe the neutropenia is being contributed by the extent of disease in the bone marrow, that's a period usually within the first 3 to 6 months on treatment, I'll be relatively liberal with growth factor support in that setting. After the marrow's been cleared, if I'm still having difficulties with neutropenia in patients on a venetoclax-based therapy, then I will dose adjust and dose reduce the venetoclax to get through the neutropenia.

If we're talking about combinations and combinations of BCL2 inhibitor plus a BTK inhibitor, the BCL2 inhibitor-based therapy, as you know, the benchmark's been set by the CLL14 trial with venetoclax plus obinutuzumab. That has sort of set our expectations for

venetoclax-based therapy with a CD20 antibody. We know the median PFS is 6 years. It is shorter for patients with high-risk features, particularly patients with 17P deletion or mutated TP53 who have a median PFS of 4 years. Patients with an unmutated immunoglobulin gene treated with venetoclax-obinutuzumab have a median PFS of about 5 years. And we don't know what the median PFS is for patients with a mutated immunoglobulin gene. So most of our newer combinations, at least in the phase 2 experience, we sort of compare them to that benchmark of what we have seen with CLL14.

There was in CLL14 a high undetectable MRD rate, and that is also a parameter that we are following for patients who are getting time-limited therapy that is venetoclax-based that correlates with longer progression-free survival, the higher proportion of patients who have achieved an undetectable MRD.

We have safely combined the BTK and BCL2 inhibitors in these combinations, and more and more we'll see more data of these combinations coming out in randomized phase 3 trials. Ibrutinib and venetoclax, there's a substantial amount of data with that combination. Those regimens mostly have treated patients for a year.

Our trial at Anderson led us to believe that perhaps patients need 2 years of treatment to optimize their outcomes with that combination. And I think the FLAIR data also, which is a randomized phase 3 trial with ibrutinib-venetoclax versus chemoimmunotherapy, that trial, the data and updates that we're seeing on it also suggests that a longer duration of treatment will improve outcomes for our patients.

And as you mentioned, acalabrutinib-venetoclax is on the NCCN Guidelines, not yet FDA-approved, and we have the triplet of acalabrutinib, venetoclax, and obinutuzumab. And as I mentioned earlier, one of the challenges with obinutuzumab has been the increased risk for infection, which was seen in the AMPLIFY trial with the triplet of acalabrutinib, venetoclax, and obinutuzumab and COVID-related events.

But these are highly effective combinations. Many patients will probably only need one treatment during their lifetime, especially if they’re in their 70s and 80s, because we're seeing very long PFS outcomes for these patients. And they don't typically need retreatment right away. If they’re progressing, they can be observed until they have indications for retreatment.

So outcomes are exceptionally good, and it's going to be more and more challenging, I think, as time goes on because we're going to have a lot of options and there's going to probably be a lot of debate about what's the optimal option.

Now let's review recent exciting data about these agents, perhaps, and focus on trials that were presented at ASH 2025. So, Matt, could you maybe review some of those highlights from ASH 2025?

Dr. Davids:
Sure. So certainly one of the highlights was the plenary session, Abstract Number 1 at the meeting, CLL17. We've been talking so far about a lot of phase 3 data sets that are comparing targeted therapies to chemoimmunotherapy. But CLL17 is really one of the first phase 3 studies that's looking at different targeted therapies compared to each other.

So this compared continuous ibrutinib to 1 of 2 different fixed-duration venetoclax-based regimens: venetoclax-obinutuzumab or venetoclax-ibrutinib. And really the follow-up is still fairly short with a median of about 3 years, but the progression-free survival at that timeframe looks similar between these different options, which does give us the confidence, even sort of with the short follow-up, that we can use these time-limited regimens and get similar outcomes for many patients compared to continuous BTK inhibitor-based strategies. Although there were some differences in the higher-risk patients, and I think it's going to be important to see longer-term data from CLL17, particularly in those groups, to see how that pans out.

So one of the challenges with CLL17 is that it is an ibrutinib-based study, and so I’ll just highlight, also, we have a trial going on called MAJIC, which is fully accrued now, which is comparing acalabrutinib-venetoclax versus venetoclax-obinutuzumab, actually with both of those having MRD-guided duration of therapy, 1 or 2 years, alluding to the point you made earlier that 1 year may not be sufficient for some patients, maybe particularly those with high-risk disease. We don't have results yet of that trial but hope to have them soon.

At this past year's ASH meeting, we also saw some of the first data for pirtobrutinib, the noncovalent BTK inhibitor, in the frontline setting for CLL. This came from a couple different studies, the BRUIN CLL-313 trial, which was a registrational trial for pirtobrutinib versus bendamustine and rituximab in the frontline setting, which showed a very clear progression-free survival advantage of pirtobrutinib. As

well as an interesting head-to-head study, the BRUIN CLL-314 trial, directly comparing pirtobrutinib to ibrutinib. The study actually included both relapsed refractory and treatment-naïve patients who were stratified in the randomization. I think both data sets were interesting in both populations, clearly showing at least that pirtobrutinib is not inferior to ibrutinib with respect to overall response rate.

We saw some very early progression-free survival data that's not really mature yet, so I think it'll be important to follow that over time. But it really does identify pirtobrutinib as an option to consider for older patients, perhaps those with cardiovascular comorbidities, even in the frontline setting. As you were alluding to before, some of these patients will only require 1 treatment or maybe 2 in their lifetime, and pirtobrutinib appears to be very safe and effective in that population.

So as we're sort of looking more toward the future, there's a lot of exciting new drugs and new combinations in development. So, Bill, maybe you can kind of briefly recap some of those data sets.

Dr. Wierda:
Yeah, so I think maybe the thing that we haven't touched on yet has been other combinations that are under investigation. Zanubrutinib has been combined with venetoclax and there is data with that combination from the SEQUOIA Arm D cohort, and that has generated high undetectable MRD rates and has been well tolerated. Sonrotoclax is a second-generation or a next-generation BCL2 inhibitor that's not yet FDA-approved but is in development in these combinations.

So as you said, a lot of interesting data presented at ASH this year. A lot of exciting data coming out. And I think this will be what we experience over the next several years with all the trials that are reading out.

And that's all the time we have today, so I want to thank our audience for listening and thank you also, Matt Davids, for joining me and for your valuable insights in this discussion. It was great to speak to you today.

Dr. Davids:
Thanks, Bill. Same. Great discussion.

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