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State of the Union: *A Targeted Approach in First-Line Treatment of CLL/SLL*

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Dr. O'Brien:
This is CME on ReachMD. And I'm Dr. Susan O'Brien. Today, Dr. Timothy Call and I will be discussing the increasing complexity associated with matching the most optimal first line therapy to a specific patient diagnosed with CLL/SLL. Dr. Call, welcome to the show.

Dr. Call:
Thank you, Dr. O'Brien.

Dr. O'Brien:
Let's get started. Dr. Call, what do we need to take into consideration when selecting a first line therapy for patients with CLL/SLL?

Dr. Call:
In the current era of targeted therapies, I try in every patient that is treatment naive to review the following factors: What is their age? What is their performance status? Very important, what are their comorbidities? Especially cardiac function or history of arrhythmia or hypertension, renal function, risk of potential tumor lysis, presence or absence of infection, presence or absence of an autoimmune complication. And what medications they may be currently taking that may require dose modification or avoidance?

The prognostic indices, such as CLL-IPI stage, may have predicted how quickly the patient got to where they need treatment, but have less to do with which treatment to choose, perhaps with the exception of 17p deletion or mutated TP53. The patient is central to the discussion.

Dr. O'Brien:
Yeah, I think the prognostic factors, as you said, are less important now, unless we're going to consider chemoimmunotherapy. Where, as you mentioned, we certainly would not want to give any type of chemoimmunotherapy to a patient with a 17p deletion or a TP53 mutation, because we know they have terrible outcomes. And it would be small molecule therapy, either with a BTK inhibitor or with venetoclax and obinutuzumab based on the CLL-14 data that led to the approval of that regimen as a frontline regimen with a fixed duration of one year.

Dr. Call:
Dr. O'Brien, with that as background, let's consider what type of patient might benefit most from available therapies. Can you walk us through the options?

Dr. O'Brien:

Sure, if we're talking about chemoimmunotherapy, the big question is: Is there still a role? And I think if there is a role for chemoimmunotherapy, it's really pretty much limited in my mind to FCR. And that means it's also limited to relatively fit patients, who have a mutated IGHV gene, because older patients have a hard time tolerating FCR. And the reason I'm limiting it to those with a mutated IGHV gene is that we know from three different trials that there appears to be a plateau on the progression-free survival curve for that group at about 55% to 60% or out 15 to 20 years, still in remission. You couldn't argue with that kind of an outcome.

However I think in this day and age with COVID, that most people are really avoiding chemoimmunotherapy. So I think we're talking about the targeted agents. There are no PI3K inhibitors approved for frontline use, so those would be limited to the relapse setting. And we really have the options of ibrutinib or acalabrutinib, both are approved as single agents, and with obinutuzumab. Ibrutinib is approved with rituximab, but we know that ibrutinib with rituximab is not better than ibrutinib alone. So I would not use rituximab at all in the frontline setting with a BTKi, I might use obinutuzumab. And then of course, as I mentioned with venetoclax and obinutuzumab being the other option, as a time-limited, one-year regimen.

We have other treatments such as CAR Ts; none of them are FDA approved for CLL. So that would really be only in the setting of a clinical trial. And then we have really exciting data that's been coming out for combining small molecules. So most of that data so far has been with ibrutinib and venetoclax, in some cases with obinutuzumab, although more data just for the oral duo with very exciting results, high degrees of MRD undetectability. And, we don't actually know how long those remissions are, we just recently got some data for three-year follow up from the CAPTIVATE trial, where over 90% of people are still in remission after only 12 months of the combination. That combination regimen is not yet FDA approved. But there is a registration study that's been completed, also showing high rates of MRD undetectability with ibrutinib and venetoclax. And so it's highly likely that that combination will become FDA approved in the not-too-distant future.

Dr. Call:
Susan, I think for most of the patients, the choices you just discussed are the primary options. There will always be those patients that you and I see who fall outside the box. But I think we're starting to see the potential of combining a monoclonal anti-CD20 antibody with either a BTKi or venetoclax.

Dr. O'Brien:
Okay, now that we've identified how we might select one or more agents for a particular patient, let's look at current guideline recommendations. So Tim, what do the NCCN guidelines say about first-line CLL treatment?

Dr. Call:
First of all, they strongly recommend that we would not treat early-stage CLL that doesn't otherwise meet the criteria for treatment unless it's in a clinical trial.

For patients who have become symptomatic, who have significant cytopenias, then they recommend consideration, such as we've recently discussed, of first-line treatment (for those without 17p deletion or TP53). Numerous recommendations that they have include acalabrutinib plus or minus obinutuzumab, ibrutinib, venetoclax plus obinutuzumab, and zanubrutinib, which is the NCCN guidelines, yet it doesn't have the FDA approval for CLL at this time. They're based on health disparity around the world. Other agents such as fludarabine-containing regimens or bendamustine-containing regimens are also considered.

For patients who are older, summarizing the NCCN, they tend to have less focus on fludarabine or bendamustine, and more on the BTKi plus or minus monoclonal antibodies, or the venetoclax/obinutuzumab-containing regimens.

For patients who have TP53 mutation, I do have a preference more for a BTK. This is based on the difference between the median progression-free survival in CLL-14 for TP53 of 49 months, whereas in the phase 2 ibrutinib study at the NCI, they have a six-year PFS of 61%. So that's one place that I would make a slight alteration. Otherwise, as you said, the recent CAPTIVATE study is very intriguing to look at finite therapy.

Dr. O'Brien:
Yes, and as I mentioned, that was just updated at ASCO for the fixed-duration cohort where everybody stopped therapy after 12 months of the combination with a three-month lead-in with ibrutinib. And in all these combination regimens, we do see this lead-in with ibrutinib plus/minus antibody. And of course the reason for that is to try and debulk the patient and minimize the risk for tumor lysis once you start the venetoclax ramp-up, and that generally works very well. And then both drugs are continued for 12 months in CAPTIVATE.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Susan O'Brien and here with me today is Dr. Timothy Call. Our focus is on achieving a better clinical understanding of the increasing complexity associated with matching patients diagnosed with CLL/SLL with the most optimal first line therapy.

The other trial that was updated at ASCO was the ELEVATE-TN trial. And that was the randomized trial of acalabrutinib, acalabrutinib plus obinutuzumab, or chlorambucil/obinutuzumab. And that update was actually quite interesting. It was a five-year update, and we already knew that both acala arms produced a longer PFS than chlorambucil-based therapy.

But what we saw at the four-year update is that those arms, in terms of PFS, had separated, and the acala plus obinutuzumab appeared to produce longer PFS, which is really interesting, because the obinutuzumab is frontloaded and it's only given for six months and then it's stopped. And yet, five years later now at this five-year update, we still see a benefit in PFS. But what was actually quite surprising to me is there appears to be an overall survival benefit emerging. Now I wouldn't be surprised that acala plus obinutuzumab produced longer survival than chlorambucil/obinutuzumab. But what's interesting is the survival difference between the two acala arms appears to be becoming significant, and again, just that six months of front-loaded antibody may be giving a survival advantage. So that was new data, the survival data, that just emerged at ASCO, which I found very interesting.

Dr. Call:
That could be practice changing.

Dr. O'Brien:
Agreed.

Dr. Call:
Dr. O'Brien, can you tell us about the key clinical trial data for BTK and BCL-2 inhibitors that helped inform our current treatment guidance for CLL?

Dr. O'Brien:
Sure. I mean, we've touched on that a bit. We now have RESONATE-2 data; eight-year follow-up was just published, I think, in the past month or two. And that trial has the longest frontline follow-up because that was the first trial, which compared ibrutinib to chlorambucil. And that eight-year data amazingly shows that with continuous therapy there is still no median PFS with ibrutinib. It was about 60% at seven years, which is really impressive that we're getting these very durable remissions with ibrutinib.

I just mentioned the ELEVATE-TN trial that was updated at ASCO. And that was the trial that led to the approval of acalabrutinib. And the way it's approved by the FDA is with or without antibody. And that was because both acala arms provided longer PFS than chlorambucil and obinutuzumab. And we've touched on the CLL-14 trial. That was the key trial that led to the approval of venetoclax and obinutuzumab in the frontline setting. And that was, again, compared to chlorambucil and obinutuzumab. And, at four years, the median PFS was not reached with VenG, and remember that's three years after completion of therapy and was about 78%. Although the median PFS for the 17p deletion, TP53 mutated patients in the venetoclax arm was shorter. And it was a little bit less than four years. So not bad considering that's after one year of therapy.

But we have long-term data now for ibrutinib that was published last year, the largest series of frontline patients with 17p deletion or TP53 mutation treated with ibrutinib. And that large series was 89 patients, which was achieved by combining frontline data from four different trials. And what that showed is that, at four years, the PFS in that group was 79%. So that's a group that—I think you were alluding to this at the beginning, Tim—where I would not want to use VenG and would actually definitely prefer to use a BTK inhibitor. Now, is it really that venetoclax/obinutuzumab is an inferior regimen in that group? Could be. But the other question would be: Is it just that stopping therapy is not a good idea? Well, the way the CLL-14 trial was designed is everybody stopped at one year, so there's no way to answer what would happen if therapy was continued. But that's, I think, the one group where I would strongly prefer using a BTK inhibitor as my frontline therapy.

Dr. Call:
Thanks. Looking at it from the standpoint of the office and the practice, I'm seeing more and more individuals are looking at wanting more shorter-term therapy. And with the current clinical trials that are going on looking at combinations of ibrutinib, obin, ven, the CAPTIVATE IV, all of the various multidrug regimens that are all going to be finite, I think that perhaps that will be one thing that we may see more of a shift to as patients, insurers, and non-insurance health payers soon to push back a bit on indefinite therapy.

Dr. O'Brien:
Right. I think that there's one small thing I'd like to touch on Tim. Would you say that the treatment is the same for patients with SLL who don't have a leukemic component as those with CLL? Or do you make any distinction between the two?

Dr. Call:
Susan, I do not make any distinction. Immunophenotypically, they are the same, they express similar mutations. I treat them the same.

Dr. O'Brien:

I agree. So do I. So this has been a great conversation. Unfortunately, that's all the time we have today. So I want to thank our audience for listening in. And thank you, Tim Call, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Call:
Thank you so much for including me.

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