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Released: 08/16/2024
Valid until: 08/16/2025
Time needed to complete: 1h 13m

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Frontline Fixed-Duration Therapy in CLL: Improving Outcomes and Tolerability

Announcer:
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Dr. Kipps:
Hello. Hi, this is CME on ReachMD, and I'm Dr. Thomas Kipps, and I'm very delighted to be joined by Dr. William Wierda, who is an outstanding investigator in this area to talk about fixed-duration therapy and when you would you consider it in the frontline setting.

Dr. Wierda:
Hi, thank you, Tom. Fixed-duration treatment, and particularly with targeted therapy, to me, that is an important strategy for a number of reasons. Now, there are some challenges with it because of the agents that we use can pose some challenges, and I'll mention that a little bit. The agent currently that we have that is the most effective in that strategy is venetoclax. There are others currently in development, but venetoclax we've had for a few years now and it is the basis for the fixed-duration regimen. The standard of care is with the addition of a CD20 antibody to venetoclax-based therapy with the objective of giving patients 6 cycles of a CD20 antibody with a year of venetoclax in the frontline setting, 2 years in the relapsed setting. And with that treatment, the objective would be to achieve a deep remission, a complete remission preferably, and an undetectable MRD state at end of treatment in both the blood and the bone marrow. If we're talking about sensitivity, that would be 10-4 or .01% level of sensitivity of testing. And with achieving that, our patients experience durable long remissions, with a median progression-free survival with venetoclax plus obinutuzumab currently now being 6 years overall. And the challenge with that strategy is really the initiation of treatment, the ramp-up that patients go through to get them up to the target dose of venetoclax 400 mg daily. Because it's such a potent drug at killing the leukemia cells, we have to monitor patients closely for tumor lysis and do a slow ramp-up. And so that's the main challenge.

We do also have patients experiencing neutropenia associated with that regimen, and that neutropenia can also be exacerbated with the CD20 antibody and CD20 antibodies are immunosuppressive, as you know. So those are a couple of other challenges with that. And many of the new trials that are ongoing, and our current trials in development, are trials with the objective of optimizing that fixed-duration strategy with venetoclax or other BCL-2 inhibitor-based therapy.

Dr. Kipps:
Would you consider using assessment of MRD [measurable residual disease] and assessing the duration of venetoclax there, because you know the FLAIR study has made a point of looking at the development of no detectable MRD, and the time from the start of therapy to that point, they're going to double down and continue venetoclax for that period of time.

Dr. Wierda:
Right. I think that the challenge with that question is that it's a little bit of a data-free zone. We don't have big clinical trials that will inform us on the best strategy for that. That's really based on our own personal experience and our own personal strategy. I know with our venetoclax-based trials, we do have patients who benefit with additional treatment beyond the fixed-duration treatment that has been

studied in clinical trials. For example, venetoclax plus obinutuzumab, or venetoclax plus ibrutinib, we know from our venetoclax/ibrutinib experience, patients can achieve deeper remissions with continued treatment beyond that first year of treatment. In fact, about half of them will convert to MRD negative from the end of year 1 to the end of year 2 of treatment. And so that's one big question with these strategies, and that is how do you optimize duration of treatment? One size doesn't fit all.

Personally, I do evaluate blood MRD, and if patients are MRD positive at the end of that first year of treatment, I do consider continuing treatment for them, rechecking MRD. If they're continuing to respond, then I will continue treatment. If they're stable, I'll also continue treatment because I don't want to get those patients off treatment too early.

Dr. Kipps:
Well, certainly there's a long way to go and I think it's very exciting to have fixed-duration therapy. Can you summarize some of the evidence that's supporting fixed-duration approaches in the frontline setting?

Dr. Wierda:
Sure. So in the frontline setting, there's the CLL14 trial; that's the big trial that we have with venetoclax/obinutuzumab that confirmed superiority over chemoimmunotherapy. There's the GAIA study, which is a 4-arm clinical trial which has 2 arms that are venetoclax-based that demonstrated superior performance with venetoclax over chemoimmunotherapy, and particularly venetoclax plus a CD20 antibody, particularly obinutuzumab. And then there are several trials with venetoclax plus ibrutinib and one randomized trial, the GLOW study, which demonstrated superiority for venetoclax plus ibrutinib over chemoimmunotherapy. And there are a number of trials, as you know, that are ongoing that will read out over the next 3 to 5 years that are venetoclax-based, fixed-duration, combined targeted therapy versus chemoimmunotherapy.

Dr. Kipps:
Currently with these fixed-duration regimens, it's exciting to note that patients can achieve very deep remissions, allowing them to do well without any additional therapy. And subsequent follow-up, of course, is always mandated to determine which patients may relapse. And of course, we'll be discussing, later, the salvage therapies that you might consider in such patients. But this is certainly an advance in the treatment of CLL with targeted therapy.

So thank you very much, Bill.

Announcer:
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