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Overcoming Disease Progression in CLL: Evidence-Based Re-Treatment Considerations

Announcer:
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Dr. Wierda:
Hi, I'm Bill Wierda from the MD Anderson Cancer Center in Houston, Texas, and this CME ReachMD session is a discussion with my friend and colleague and mentor, Dr. Thomas Kipps from UCSD. And we're going to be reviewing options for re-treatment, or considerations for re-treatment, for a patient who has failed treatment.

Tom has a case that he's going to review for us. So, Tom?

Dr. Kipps:
Well, thank you, Bill. It's great to be with you. Yes, this is an interesting case of a 66-year-old man who was diagnosed with CLL. He did have features of unmutated immunoglobulin genes, and he had also trisomy 12 as a solo cytogenetic abnormality. Because of rapidly progressive disease with a doubling time of 4 months, he received treatment with bendamustine and rituximab one year after his diagnosis and achieved a complete remission by iwCLL criteria. Due to relapsed progressive disease 2 years later, though, he presented to us for therapy. FISH at that time demonstrated he had a complex karyotype with trisomy 12 and deletion 17p. We also identified a glycine to serine substitution at position 244 and TP53, so TP53 gene was mutated. He was treated with 6 cycles of obinutuzumab and venetoclax after he received debulking therapy of high-dose methylprednisolone and did quite well. A year after he initiated therapy with venetoclax, he achieved a complete remission. His marrow biopsy in October of 2018 showed no evidence of CLL by morphology, but we detected MRD at a .02% by 10-color flow cytometry. So we opted to continue venetoclax at 400 mg a day.

He did well, but then about a year later, he developed more rapidly progressive disease with lymph node enlargement. We evaluated him. He again was found to have the same complex karyotype with trisomy 12 and deletion 17p with the same mutation in TP53. However, we noted a new mutation in BCL-2 that substituted alanine for proline at position 113, and we noted that that actually could impair the capacity of venetoclax to bind BCL-2.

So the question, I guess, where do you take this case from here? And I think this is an important discussion as we find patients who may become resistant to targeted therapies.

Dr. Wierda:
Yeah, so this is an interesting case. It's a case of a very aggressive CLL. A 66-year-old gentleman who has just 2 years of remission with BR [bendamustine plus rituximab] after achieving a complete remission and progresses with 17p deletion. So that would lead me to speculate maybe the 17p was there before he even got the chemoimmunotherapy, and you selected for that with the treatment that he got. And he got venetoclax and responded to venetoclax, but as you noted, is MRD positive, and that's the rationale for continuing treatment with venetoclax.

Now we do continue treatment anyway for 2 years in the relapsed setting with venetoclax-based therapy, which is the setting that this patient received venetoclax in. This patient also got obinutuzumab, which in my opinion is a better CD20 antibody. The MURANO trial, which studied venetoclax in the relapse setting, used rituximab, but my opinion is that there's substantial data that supports use of obinutuzumab over rituximab. And so there are there are a number of important features for this case and it is an aggressive case of CLL, and so maybe you can comment on what the next steps were for this patient in terms of his management.

Dr. Kipps:
Well, he actually opted to have therapy with a BTK inhibitor, which we initiated on him. At the time, we started him on ibrutinib, and we continued venetoclax for about a month overlap. We did not want to stop venetoclax and have any hiatus in therapy, recognizing the aggressive nature of his disease. And he actually did quite well, achieving a reduction in his lymphadenopathy with really excellent disease control. We later switched to acalabrutinib because of some cardiac abnormalities that he developed, and he did well for a period of time after maybe a couple of years of therapy. However, he again developed resistance to the covalent inhibitors and developed now a new C481S mutation requiring that we switch him to a non-covalent inhibitor, pirtobrutinib.

Unfortunately, after 9 months of ibrutinib, he developed yet another mutation at 474 and absent, though, was the mutation that we saw at 481. So this represents the plasticity of the disease, sometimes trying to outsmart even the best of targeted therapies. And so we're probably going to have to do this. But I do think it highlights the importance of following your patients closely with evidence of these new mutations that might confer resistance to these targeted therapies.

Dr. Wierda:
Maybe, Tom, you can comment also on what the long-term plan might be for this patient at this point.

Dr. Kipps:
He's been evaluated by the transplant group, but it seems that he's more appropriate and he's actually now being screened for a CAR T-cell therapy. And I think this is the way we have to go because of his resistance to targeted therapy. Certainly, with his mutation and 17p deletion, he is not a candidate for chemoimmunotherapy. So currently we have him on therapy with duvelisib, which is a drug that inhibits the PI3 kinase delta gamma isoform. He's doing well but is developing complications related to duvelisib therapy. In addition, we treated him with obinutuzumab in conjunction with duvelisib. We're hoping to maintain disease control so he can undergo CAR T-cell therapy.

Dr. Wierda:
Well, thank you, Tom, for an excellent discussion and a very complicated case and thank the audience for tuning in. We hope that this discussion was helpful and useful in your practice.

Dr. Kipps:
Thank you, Bill.

Announcer:
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