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Combination Therapy in CLL: Identifying the Right Patient for the Right Treatment Approach

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Dr. Kipps:
Hi. This is CME on ReachMD, and I'm Dr. Thomas Kipps. I'm joined today by Dr. Bill Wierda at MD Anderson, and he has to share with us a case vignette on some cases that commonly are seen that we'll discuss in the upcoming discussion.

Dr. Wierda:
Thanks, Tom. I'm going to briefly go through the case. It's a 70-year-old gentleman who'd been monitored for 5 years with observation after his initial diagnosis of CLL. His prognostic factor profile done at the current time is that he had a 13q deletion by FISH, an unmutated immunoglobulin gene, and sequencing for TP53 revealed wild-type TP53. He has Rai stage III disease by virtue of having a hemoglobin of 10.9. His white count was 90,000 and his platelet count was 110,000. He has some palpable nodes in his cervical, axillary, and inguinal regions, measuring 1 to 3 cm and bilaterally. And he had progressive symptoms over the past 6 months with escalating fatigue and reduction in his activity levels some mild night sweats occurring with regularity, once to twice a week, and no fever or unintentional weight loss. He has normal renal function, a history of medically managed hypertension, hyperlipidemia, type 2 diabetes, and coronary artery disease requiring stenting 3 years ago. And because of his progressive symptoms, he comes in to talk about what to do next and what are his treatment options.

Dr. Kipps:
Well, thank you for that, Bill. I think that this case certainly is one of a patient who is in need of therapy. Now the question is, what type of therapy would you recommend? I think, notably, he does not have the mutations in TP53 or deletion in the short arm of chromosome 17 that potentially, I guess, could make the use of chemoimmunotherapy possible. However, clearly with the advent of targeted therapy and the improved outcomes with targeted therapy, one has to maybe put that in mind. I suppose one of the aspects there is whether to use a continuous therapy with an inhibitor of BTK or maybe to consider a fixed-duration treatment using drugs such as venetoclax which inhibit BCL-2, in conjunction with an anti-CD20 antibody.

One of the things that you have to bear in mind is the patient's medical history. I take very seriously if they have a history of hypertension, coronary vascular disease, then they may also have other problems too that make them at higher risk for atrial fibrillation or other cardiac arrhythmias. And I think as a class effect, the inhibitors of BTKi, particularly the covalent inhibitors, are associated with a slightly increased risk of atrial fibrillation. I do believe these medications don't cause it directly but lower the threshold for atrial fibrillation in patients who may have a predisposition for that. We typically like to have the patients evaluated closely by cardiology, perhaps to do an echocardiogram, look for evidence of left ventricular hypertrophy or left atrial enlargement. These factors are associated with the predilection for atrial fibrillation. One has to be extremely cautious then when considering some of these covenant BTKis for treatment.

There's notable differences between the different covalent BTKi in terms of the relative risk of atrial fibrillation, but all seem to have

some increased relative risk of atrial fibrillation over that of patients treated with chemotherapy in many of the phase 3 clinical trials. So I think this is something that has to be borne in mind. On the other hand, the fixed-duration therapy has its other problems in terms of the need to extensively treat the patient with drugs such as obinutuzumab, requiring IV infusion, plus venetoclax, which requires attention to, as you mentioned, the incidence of tumor lysis with the initiation of therapy. But that may be an attractive option for this particular patient.

I think that there are good options in both cases.

Dr. Wierda:
In this case, when I sit down with the patient, we talk about what the patient's preference is, also, with a discussion about and understanding about what those 2 treatment strategy options involve. Maintenance therapy with the BTK inhibitor means lifelong, essentially, treatment. This patient's 70 and should have at least a decade more of good quality life ahead of him, which, if he goes on a BTK inhibitor, would involve taking daily medication with potential for side effects and toxicities associated with the BTK. We didn't talk about specific BTKs, but the preference would be for a second-generation BTK because of the lower incidence of cardiac toxicities, particularly atrial fibrillation associated with those second-generation acalabrutinib and zanubrutinib.

My preference is for patients to be in a good, deep remission and off treatment. And so I would probably advocate, when I have the discussion with this patient, for venetoclax-based therapy. That would require a year of venetoclax plus the 6 months of the obinutuzumab, as you mentioned. And following that, remission. Now, the patient has an unmutated immunoglobulin gene, so we would talk about the fact that on the CLL14 trial, the median progression-free survival for patients with an unmutated immunoglobulin gene is 5 years, so 4 years of remission. And after that, we might be again talking about re-treatment with whatever's new and effective at that time or re-treatment with venetoclax-based therapy. But I do expect that there will be advances in progress between now and 5, 6 years from now, so we would be talking about different options in that setting.

So, again, my preference is for fixed-duration treatment, and I usually am advocating for a venetoclax-based therapy, whether it's standard of care or on a clinical trial.

Dr. Kipps:
Well, thank you, Dr. Wierda, for that excellent discussion, and I thank the audience for tuning in. We hope this discussion is useful for your practice.

Announcer:
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