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CAR T and Bispecifics in LBCL: Redefining Second-Line Therapy Choices

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the evolving role of bispecific antibodies in the treatment of large B-cell lymphoma and their effect on current sequencing paradigms is Dr. Samuel Yamshon. He's the Director of the Cellular Therapy Service and an Assistant Professor of Medicine at Weill Cornell Medicine in New York. Dr. Yamshon, welcome to the program.

Dr. Yamshon:
Yeah. Thank you so much for having me and looking forward to what I think is an interesting discussion.

Dr. Turck:
Well, to start us off, how would you describe the evolving role of bispecific antibodies in second-line settings today?

Dr. Yamshon:
Well, I think one thing that's very exciting right now in diffuse large B-cell lymphoma is that we have a lot of different options for patients that seem to be very effective, which is what we care about. We've had CAR T-cells in the second line for a few years, but the bispecifics are new players on the scene in the second line. And what we've seen in the last couple of years have been these bispecific antibody trials in combination with chemotherapy—whether it's true chemotherapy like the glofitamab GemOX combination, the epcoritamab/GemOX combination, or in combination with an antibody drug conjugate like the Mosun and Pola study—but what we've seen in these second-line studies of bispecific antibodies is that we do see some impressive efficacy in what can often be somewhat of a difficult patient population to treat, especially for patients who might not be eligible or might not be able to receive CAR T-cell therapy in the second line. And so one thing that I'm always excited about is having effective options that give us a lot more flexibility in terms of treatment schedule, toxicity profile, and patient preferences. And also, even in terms of thinking about patients who will eventually go on to CAR T-cells, it gives us a lot more bridging options as well. And so I think that these studies of bispecifics in the second line have been practice-changing for me, personally.

Dr. Turck:
Now, if we take a look at some of the clinical data driving some of the changes that we've been discussing, epcoritamab showed durable responses in the EPCORE NHL-1 study, with a median duration of response of 36.1 months and progression-free survival of 37.3 months. Another option, glofitamab, was approved by the FDA in 2023 and offers a fixed-duration alternative. And the SUNMO Phase 3 trial showed a 59 percent reduction in progression or death with mosunetuzumab combined with polatuzumab/vedotin compared to art/GemOX.

So with all that being said, what kind of impact are these data having on your approach to second-line treatment?

Dr. Yamshon:
Yeah, so just a couple of things that I think are important to separate. One is that the single-agent studies of epcoritamab and glofitamab were for patients with diffuse large B-cell lymphoma who were treated in the third line or greater, and so currently, those drugs are

approved in the third line, whereas the combination studies—the epcoritamab/GemOX study and then the STARGLO study in which glofitamab was combined with GemOX as well—were in the second line. And still, when I'm using those two agents in the second line, I typically do them as they were done in the clinical trials, which is combining them with chemoimmunotherapy. One advantage that it gives is that I think we all agree that the bispecific is the drug that's doing the heavy lifting, but the chemotherapy is actually very helpful in the beginning to get patients over the hump while the bispecific antibodies are ramping up. So it almost allows you to debulk with the chemo while the bispecifics are getting ramped up, and then later on, the bispecifics are the ones that are doing the heavy lifting. And what that often will allow us to do is actually potentially even drop the chemotherapy portion and stick with just the bispecific based on those results.

Dr. Turck:
And from a pharmacologic or biologic perspective, how might bispecifics outperform CAR T-cell therapy in certain patients?

Dr. Yamshon:
So I think when you go and look at the survival curves for patients who receive CAR T-cell therapy, CAR T-cell therapy—I think we all agree—is curative intent therapy. But the dynamics of the patients who relapse are very interesting in that in diffuse large B-cell lymphoma, for patients who get CAR T, the majority of patients respond, and actually, many patients have complete remissions on the first PET scan. And so CAR T has one of the highest overall response rates of relapse in relapsed refractory DLBCL of any treatment, and certainly, the CR rates are incredibly high as well.

But what's interesting is that many patients do still relapse, and typically, those relapses occur early. And so in patients who relapse with CAR T, the majority occur in the first 3 months, and nearly all of them occur in the first year. And so part of that, I think, is related to the T cell dynamics and that those CAR-T cells are getting exhausted and then allowing the lymphoma to come back.

So one advantage that I think bispecific antibodies could have from a mechanistic perspective and a biologic perspective is that they are a long-term treatment, even for fixed-duration treatments—glofitamab treatment continues for a year and then epcoritamab is a continuous treatment on a treat-to-progression basis. You're continuing to engage those T cells against lymphoma over time, which could, I think, allow the immune system to keep that lymphoma in check, whereas with CAR T, in theory, if the lymphoma breaks free early, then you end up behind the 8 ball.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck and I'm speaking with Dr. Samuel Yamshon about how bispecific antibodies are reshaping the second-line treatment of large B-cell lymphoma.

So, Dr. Yamshon, when you're considering whether to use CAR T or bispecifics in the second-line setting, how do patient-specific factors like comorbidities, access, or institutional readiness shape your decision?

Dr. Yamshon:
The question of CAR-T eligibility is really critical, and the reason why I frame it in that way is that with a disease like diffuse large B-cell lymphoma, it is a curable disease, and so our goal should always be curative intent. And so when I'm evaluating a patient, I am trying to prioritize getting them to a cure. And currently, CAR T-cells have proven themselves to be a curative-intent treatment. And while bispecific antibodies are very effective and may well, I think, eventually prove to be curative, we don't yet know that they are curative. And so because of that, I do try to reach for CAR T as my potential first option for patients who I can get to CAR T.

But for a lot of patients, we're not able to do that, and there are many different reasons why that might be. There are sometimes disease-related reasons. They have very rapidly progressive disease, and we're not able to get insurance authorization in time to collect them, and they need a treatment right now. Other reasons might be limited caregiver support. Patients do need to be seen everyday post-CAR T infusion for the first 1 to 2 weeks, and at many centers, that initial 7-day window is still done entirely in-patient, and so there are a lot of social barriers that could prevent someone from going to CAR T in the second line. And then for many centers, slot availability or insurance issues can prevent prompt access to CAR T-cell therapy.

And so in many of those cases, I am reaching for bispecific antibodies in the second line, even in the patients who I think may be medically eligible for CAR T, to try to get their disease under control or potentially even as the primary treatment.

Dr. Turck:
Now, despite their potential benefits, bispecifics, like any treatment option, are not without their challenges. So what are some of the key safety concerns and any other obstacles that we need to be aware of?

Dr. Yamshon:
Bispecific antibodies are interesting compared to some of our other treatments in DLBCL in that, like CAR T, they use the immune response against the lymphoma. And so they do have the potential for cytokine release syndrome and neurotoxicity, just like the CAR T cells do. But luckily, the rates of any-grade cytokine release syndrome or neurotoxicity, and certainly for high-grade cytokine release syndrome and neurotoxicity, are incredibly low. And so these are treatments that are usually safe to be given in the clinic. For some of the bispecifics, one of the step-up doses is recommended to be given inpatient. But for the most part, these are very manageable drugs in the short-term.

What's interesting is we talked a little bit earlier about the mechanism of continuing to harness those T-cells over time. And against the lymphoma, that certainly has a potential mechanistic benefit. But we also find that with the bispecific antibodies, there is a risk of immunosuppression, which of course, as oncologists, we're very used to our drugs being immunosuppressive. But I find that with the bispecific antibodies, immunosuppression can be surprisingly severe. And in patients who on long-term bispecific antibodies, I often find that people are getting recurrent upper respiratory infections and potentially even bacterial infections.

Our myeloma colleagues using bispecific antibodies—just as a blanket rule—give IVIG to everyone. And of course, it's a different disease; you're targeting plasma cells. But I think that in the lymphoma world, we may be able to learn something from our myeloma colleagues, and since I've started using bispecific antibodies, I have had a much lower threshold to reach for IVIG and have been much more aggressive about prophylaxis and things like that in these patients than I was at the beginning.

Dr. Turck:
And if we look ahead before we close, Dr. Yamshon, do you see any potential for bispecifics to move even earlier, say to frontline therapy or maintenance strategies?

Dr. Yamshon:
Definitely. And I think we're all very excited about the potential for bispecific antibodies in the frontline setting in various capacities. There are several trials out there right now of bispecifics plus R-CHOP or plus Pola-RCHP in the frontline that we're anxiously awaiting the readout of. And some have even already been published. There was a mosunetuzumab plus R-CHOP backbone study that was published in *Blood Advances* earlier this year.

Another area that I think is very exciting in the frontline setting is for patients who might not be able to tolerate anthracycline treatment. Typically, our standard of care has been R-mini-CHOP, which is just not as effective as we would like it to be. And so there are some very promising studies of the bispecific antibodies like epcoritamab as a single-agent that was presented at ASH last year at the frontline in anthracycline-ineligible patients or in combination. I think definitely we're going to be seeing a lot more of bispecifics in earlier lines over the next few years, as we should because I think they're very effective drugs in the right setting.

Well, as those comments bring us to the end of today's program, I want to thank my guest, Dr. Samuel Yamshon, for joining me to discuss the impact of bispecific antibodies on the current and future treatment of large B-cell lymphoma. Dr. Yamshon, it was great having on the program.

Dr. Yamshon:
Thanks for having me.

Announcer:
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