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Sequencing Decisions in R/R LBCL: CAR T-Cell Therapy and Bispecific Antibodies

Announcer:
You're listening to *Project Oncology* on ReachMD. This episode is sponsored by Bristol Myers Squibb. This is a non-certified educational series produced and controlled by ReachMD. Here's your host, Dr. Steve Jackson.

Dr. Jackson:
This is *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and joining me to discuss the sequencing of CAR T-cell therapy and bispecific antibodies in patients with relapsed or refractory large B-cell lymphoma are Dr. Paolo Caimi and Dr. Naren Epperla.

Dr. Caimi is the Associate BMT and CT Director for Cellular Therapy at the Cleveland Clinic Cancer Institute and an Associate Professor in the Department of Medicine at the Case Western Reserve University School of Medicine. Dr. Caimi, welcome to the program.

Dr. Caimi:
Thank you. Glad to be here.

Dr. Jackson:
Also joining us is Dr. Epperla, who's an Associate Professor of Medicine and Associate Chief of Clinical Research in the Division of Hematology at the University of Utah Huntsman Cancer Institute. And Dr. Epperla, thanks to you for being here today as well.

Dr. Epperla:
Pleasure to be here.

Dr. Jackson:
To set the stage for this conversation, Dr. Caimi, how do current practice guidelines position CAR T-cell therapy and the bispecific antibodies across the second- and third-line treatment of relapsed or refractory large B-cell lymphoma?

Dr. Caimi:
Over the last five years, or now close to a decade, with the emergence of CAR T-cell therapy, and particularly with its approval in the second line for patients with early relapse—that means less than a year after completing initial chemotherapy—the CAR T-cell therapies have become the preferred therapy for those who can access them or who can tolerate them, which is probably a larger number of patients than those who can tolerate autologous transplant. And over the last few years, with the emergence of bispecific antibodies, the patients who are considered ineligible for CAR T-cell therapy in the same circumstances have progressively been treated with combinations of bispecifics. But that means that for the patients who are eligible for CAR T-cells, that is the modality of preference.

However, with increasing efficacy observed with bispecific combinations in particular, such as glofitamab combined with oxaliplatin and gemcitabine, mosunetuzumab-polatuzumab, or glofitamab-polatuzumab, those combinations have shown high grades of efficacy, and we usually consider them as good options for patients who cannot access CAR Ts or who cannot tolerate CAR Ts.

Dr. Jackson:
Dr. Epperla, what recent clinical evidence is most important for understanding how the second- and third-line treatment landscape is changing for relapsed or refractory large B-cell lymphoma?

Dr. Epperla:
Given the efficacy of CAR T in the third line and poor outcomes with high-dose chemotherapy and autologous stem cell rescue in the second line, three phase III randomized controlled trials were undertaken: ZUMA-7 for axi-cel, BELINDA for tisagenlecleucel, and TRANSFORM for liso-cel. Both ZUMA-7 and TRANSFORM showed superior event-free survival compared to the standard-of-care arm.

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In fact, the long-term follow-up data for ZUMA-7 actually showed that axi-cel demonstrated superior overall survival benefit at four years compared to the standard-of-care arm, further establishing the role of CAR T in second-line large B-cell lymphoma for primary refractory and early-relapse large B-cell lymphoma patients.

Bispecific antibodies as monotherapy have also received approval in third-line large B-cell lymphoma. And more recently, in second-line large B-cell lymphoma, there has been an increased use, especially in transplant-ineligible patients, based on the recent phase III randomized controlled trial with Glofit-GemOx compared to R-GemOx.

Given all these options, I think it is important to take into account patient and disease characteristics while choosing CAR T or bispecific antibody therapy.

Dr. Jackson:
And Dr. Caimi, how do treatment attributes like speed of disease control and expected durability of response and treatment course factor into your sequencing decisions?

Dr. Caimi:
I think all of those factors are very important to take into account. The speed of disease control is probably very important for bispecifics, a single agent, and CAR T-cell therapy. For CAR T-cell therapy, because you have to wait usually two to three weeks to be able to receive the therapy from the moment of apheresis. And for bispecifics, you require a dose escalation or ramp-up until you reach the first effective dose, which is usually between two and three weeks. And in the case of CAR Ts, the time to receive insurance approval adds an additional amount of time. So you can envision a patient that has rapidly progressive disease who cannot wait for either a bispecific to take hold of the disease or a CAR T-cell therapy to be administered in time to be able to control the disease.

So this is where the combination of bispecifics with cytotoxics or with antibody-drug conjugates really comes into play, because they can achieve the benefit of the immunotherapy, immune effector, and T-cell redirect therapy of the bispecific, but for the immediate benefit of rapid disease control, the chemotherapy or the antibody-drug conjugate can help with that.

The durability of response also is important. I think it's established now that a significant percentage of patients who are treated with CAR Ts have long-lasting remission, even though another significant portion of patients will relapse. And this is where other combinations need to demonstrate that they can achieve disease control that exceeds 40 to 50 percent in the first year.

And finally, the treatment course is very important for patients in terms of their logistics. A CAR T will require the patient to occasionally stay in the hospital many times or be monitored very closely and receive chemotherapy conditioning or lymphodepletion a few days before, plus the prior apheresis. So it requires multiple visits and continuous evaluations. Very frequent hospitalization is needed if you get side effects. For bispecifics, the treatment is weekly for the first few weeks, and then biweekly for certain ones, and every three weeks for others, and sometimes it's continuous and can be prolonged in many scenarios. So the patients are having very frequent visits. I think those are really important to take into consideration when you're choosing therapy and also when you're sequencing them.

Dr. Jackson:
And Dr. Epperla, let's discuss disease characteristics like tumor burden, pace of progression, timing of relapse, and response to prior therapy. Which are the most important when sequencing CAR T-cell therapy and bispecific antibodies in this population?

Dr. Epperla:
I think all of these factors are equally important. But if I have to choose the most important one, in my opinion, I would say timing of relapse probably takes the first choice here. And the reason for that is because we have high-quality data in the form of phase III randomized controlled trials where patients were randomized to the CAR T-cell therapy or the standard of care, which was high-dose chemotherapy and autologous stem cell rescue, clearly showing event-free survival and overall survival benefit. So for patients who are early relapse and primary refractory, my go-to option would be CAR T, of course, considering other factors as well, which I'll talk about in a second.

The other thing to keep in mind regarding timing of relapse is while choosing bispecific antibodies, it is very important to think about the timing of relapse post-CAR T. Patients who relapse within three months following CAR T usually do not respond to bispecific antibodies compared to those who received bispecific antibodies beyond six months after CAR T. And the reason for that is because for bispecific antibodies to work, you need the host T cells to be fit. And if the patients have relapsed quickly, there is a T-cell exhaustion phenotype, which tends to really hamper the activity of the bispecific antibodies.

All the other factors are a close second. If I go over the pace of progression, the autologous CAR T-cell therapies usually take anywhere between two to four weeks for manufacturing turnaround for vein-to-vein time, depending upon the type of CAR T product we are talking about.

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And if patients have rapidly explosive disease or impending organ failure, and if systemic bridging therapy cannot safely stabilize the disease, I think initiating autologous CAR T can become logistically challenging.

Response to prior therapy is an interesting point. It's very rare in the current day and age to see that patients have not been exposed to either a CAR T or bispecific antibody in a relapse setting. In the rare instance of a multiply relapsed diffuse large B-cell lymphoma patient who has not seen either of these products, I would usually suggest biopsying it to see whether they have CD19 expression or CD20 expression and then making a decision based on those results of the biopsy. Also, refractoriness to immediate prior therapy should be taken into consideration while choosing one of the two options.

Dr. Jackson:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Drs. Paolo Caimi and Naren Epperla about treatment sequencing in relapsed or refractory large B-cell lymphoma.

Dr. Epperla, which patient-specific factors, such as functional status, comorbidities, organ function, tolerance of prior therapy, et cetera, can influence how you sequence CAR T-cell therapy and bispecific antibodies?

Dr. Epperla:
If we go one by one, let's talk about functional status and frailty. I always believe it is very important to make it clear what is driving poor functional status. So if the disease is driving poor functional status, then I think they definitely can receive CAR T-cell therapy. If they already have a poor baseline prior to their disease, then that's a different story, and that's a different phenotype we are talking about.

The other thing to keep in mind is organ function and specific comorbidities. Again, the few organ dysfunctions that I quickly can think of are the renal reserve and cardiovascular and pulmonary reserves. Significant renal impairment alters fludarabine clearance and can increase hematological toxicity. And the reason for that is because most of these autologous CAR T-cell therapies that are currently approved involve lymphodepleting chemotherapy. Bispecific antibodies do not require any lymphodepletion, making them easier to administer in these patients with baseline renal or hepatic impairment. Similarly, in patients with baseline cardiac or pulmonary dysfunction, there is an increased risk of organ decompensation during CRS. Of course, this is applicable to both CAR T and bispecific antibodies, but something to keep in mind for patients receiving CAR T-cell therapy.

Moving on to the tolerance of prior therapy, patients who develop prolonged cytopenias or severe infectious complications during previous chemoimmunotherapy regimens may have limited bone marrow reserve. So cytopenias can further be prolonged following CAR T-cell therapy due to lymphodepletion and immune activation. So it’s something to keep in mind in patients who have received several lines of treatment and are cytopenic. Bispecific antibodies, on the other hand, depend on patients’ existing endogenous T cells. So patients who have suffered severe immune depletion from multiple immediate prior lines of cytotoxic chemotherapy or purine analogs may exhibit endogenous T-cell exhaustion, which can reduce both the depth and durability of response to bispecific.

Dr. Jackson:
Dr. Caimi, when more than one treatment approach may be clinically feasible, how do patient preferences and practical considerations influence your sequencing decisions?

Dr. Caimi:
Most of our initial recommendations are based on the clinical factors and the conditions of the disease, and then the practicalities come into play. One of them, I think, probably when we're offering CAR Ts, traveling to the center, staying within a specific distance from the center for a period of time, and having a caregiver for that period of time who can be responsive in case there's complications can be important for many patients who don't have a broad social network that can support them during that period of time.

For bispecifics, the main practical consideration is that the infusion is also done in centers that are similar to those where CAR T are done, and patients require repeat travel to those centers. So the distance to the center where we're administering the therapies is probably the number one consideration besides insurance and coverage factors.

The other scenarios that you have to think of are, are these patients going to return to their site of origin and we're going to continue to monitor them distantly, or are they going to just proceed with subsequent therapies there? And also in general, if they're going to have specific needs after their care, particularly if they have complications. For some patients, it's easier to be closer to the center where they're administering and then return home once they're done, like you would do with the CAR T cells. And for other patients, it's easier to just come for a few days at a time, get hospitalized sometimes for the dose escalation in the bispecific, and return to the initiating center where they can continue the treatment once the dose of the bispecific is established.

Dr. Jackson:
Dr. Caimi, when you tie those clinical patient and practical considerations together, how do you see the approach to sequencing CAR T-

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cell therapy and bispecific antibodies evolving across second- and third-line treatment in this population?

Dr. Caimi:
I think evolution is probably the main word for the treatment of large B-cell lymphoma for this and maybe the next decade. And you can think that whereas we were talking about only being able to give CAR Ts with curative intent at very specialized centers at the beginning of the decade, now that we've been moving towards 2030, we're seeing that CAR Ts can be given in the outpatient setting. Maybe we'll be able to give CAR Ts at a lower cost setting, like an outpatient, or even easier, at a center distant from a specialized location.

With the emergence of bispecific combinations, we have had observations that probably suggest that you can offer something in the second line or third line that has outcomes very similar to those of CAR T cells, hopefully, that would bear truth in the subsequent trials. And in that scenario, it will mean that we'll have more alternatives for patients who can choose based on their reality. And also, we can choose based on the opportunities for controlling their disease in the most efficacious and better tolerated fashion.

Dr. Jackson:
And as we look ahead, Dr. Epperla, what emerging evidence do you think will be the most important in shaping how CAR T-cell therapy and bispecific antibodies are used across second- and third-line relapsed or refractory large B-cell lymphoma?

Dr. Epperla:
There are several key categories of emerging clinical evidence that will shape sequencing. First, I want to start off with the front-line bispecific integration. Clinical trials are actively evaluating bispecific antibodies integrated into first-line chemoimmunotherapy platforms. And there are ongoing phase III randomized controlled trials, which will throw light onto it. If frontline bispecific strategies succeed, then the biological background of relapsed disease will change, and relapsing T cells may exhibit baseline T-cell exhaustion or tumors may show altered CD20 target density, changing how second-line approaches will be used. Maybe this will change in the future, but to date, the data we have is from retrospective studies, pooled analyses, and meta-analyses. What we learned from those studies is that a bispecific antibody continues to remain effective after CAR T-cell therapy, and that CAR T-cell therapy is still a viable option even after prior bispecific antibody exposure.

And the other thing which is very important to keep in mind is that there have been multiple schools of thought about whether we can use bispecific antibodies as bridging or if they should only be used as a destination therapy. Again, there is small-scale retrospective data from meta-analysis and pooled analysis showing that bispecific antibodies can be used as bridging therapies. But I would also offer caution that there are ongoing trials that would throw light on this, and not read too much into the data that we have.

Also important to keep in mind is that the dual targeting and off-the-shelf cellular platforms are also gaining traction. So there are ongoing trials with dual-target CAR Ts, which are CD19/CD20 and CD19/CD22, against standard-of-care CD19 autologous CAR T. And this is important because that will really help us define what is the best approach in the second line.

The talk will not be complete if we don't talk about the allogeneic CAR Ts and in vivo CAR Ts. One of the major limitations of current autologous CAR T-cell therapies is the manufacturing time. And if you have off-the-shelf CAR Ts or in vivo CAR Ts, you're essentially negating this manufacturing turnaround time and increasing the T-cell fitness and stemness, if you may, which will hopefully further improve the outcome.

And lastly, it will not be too far away when we start using MRD-adapted approaches. So data on circulating tumor DNA dynamics during fixed-duration bispecific antibodies or CAR T-cell therapies have shown that early post-treatment MRD negativity correlates with long-term progression-free survival. So MRD kinetics are already increasingly being used in clinical trial design to dictate whether treatment can safely be discontinued or if early consolidation is needed.

I would conclude by saying the integration of CAR T-cell therapy and bispecific antibodies in second-line, third-line, or later relapsed or refractory large B-cell lymphoma has truly shifted from a competition to a complementary sequencing strategy.

Dr. Jackson:
That's a great way to round out this discussion. I want to thank Drs. Paolo Caimi and Naren Epperla, for joining me to share their perspectives on the decision-making around sequencing CAR T-cell therapy and bispecific antibodies in relapsed or refractory large B-cell lymphoma.

Dr. Caimi, Dr. Epperla, it was great speaking with both of you today.

Dr. Caimi:
Thank you.

Dr. Epperla:

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Thank you.

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