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Panel Discussion: Selecting and Sequencing CD19-Targeted Therapy in the Second-line Treatment of R/R DLBCL

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Dr. Caimi:
Hello, I am Paolo Caimi from Cleveland Clinic, and I am here with Dr. Peter Riedell from the University of Chicago to discuss the sequencing and treatment of patients with relapse and relapse refractory large cell lymphoma with CD19 therapies. So, we will start with, with a case and discussing primarily focused on the on the second line therapy of patients with relapse and refractory large cell lymphoma. And I will, you know, try to connect with a patient that I've seen recently in clinic. This is an 83-year-old gentleman who was diagnosed approximately four years ago with a diffuse large b-cell lymphoma treated, actually presented with a retroperitoneal mass that was localized in several, multiple spots in the retroperitoneum treated with 6 cycles of R-CHOP. He achieved a complete remission and had done very well except for the fact that he needed a quadruple bypass approximately 24 months ago, but he's otherwise functional. And he actually had a CT scan done for other reasons and was found to have a recurrent mass approximately three weeks ago. He's not symptomatic, very functional but also on repeat PET scan, he also has, he has a base of tongue mass as well as cervical lymphadenopathy. We had a biopsy of that and it demonstrates recurrence of his diffuse large cell lymphoma as well as involvement of, of his vertebra. So, in this scenario, Dr. Riedell, of a patient that has relapsed several years after the previous treatment with the other fact that they've aged now close to 83 years of age, and they've had some comorbidities, how would you approach the choice of second-line therapy at this stage?

Dr. Riedell:
Yeah, so this is, certainly, the answer to this has evolved recently. And thankfully now we have a little bit more tools in our toolbox to be able to use for patients like this. So, the standard treatment paradigm in certainly younger and fit patients with relapsed refractory large cell lymphoma would be to challenge them with platinum-based salvage chemoimmunotherapy and then if responsive, move them into an autologous stem cell transplant. But generally, that's not a preferred practice pattern for patients who are of advanced age or those that have comorbidities. Recently, we've had a few different studies which have been published, evaluating car T-cell therapy in the second line. One of those studies was the pilot trial which actually looked at the use of lisocabtagene maraleucel in patients that were of advanced age and really not felt to be candidates for an autologous stem cell transplant. And that was a single-arm phase-two trial. And actually, it showed very encouraging results in that population of patients with response rates around the 80% range and CR rates around the 50% range. And based on results of the pilot trial actually, lyocell cell did garner a second-line approval for patients with relapse or refractory disease, and really, they're not candidates for autologous stem cell transplant. So, there's no time criteria in terms of needing to be an early relapser versus a late relapser. And so, I think in my eyes that would be the preferred treatment approach in this patient, you know, should they be, felt to be a candidate. And I think, you know, you did bring up some relevant medical comorbidities in this patient including their coronary artery disease. They needed a coronary bypass graft and certainly, their advanced age might make this therapy a little bit challenging for the patient. But, you know, if we look to the results of the pilot trial, they did

include patients with comorbidities. You know, patients needed to meet at least one criteria for being ineligible for autologous stem cell transplant. And that included things like impaired cardiac function, impaired renal function, advanced age, and impaired pulmonary function. And so, you know, that obviously suggests that the patients included in that trial did have some medical comorbidities. And so, I think that this person would certainly, you know, meet those eligibility criteria and potentially be a candidate for that trial. And so that would make me feel a little more comfortable providing that type of therapy. And, and the other thing I think to be mindful of is how symptomatic that patient would be at the present time when you're evaluating them for relapse disease.

You know, based on what you were relating in your history, it seems like this was noted a little bit incidentally, based on imaging, and so that may suggest that this is a little bit more of a indolent relapse or relapse that was caught a little bit early and that may afford us the time to get insurance approval and to move forward with car T-cell collection manufacturing and so forth. But, you know, if we were to imagine an alternate scenario, a lot of times these patients may have more advanced and aggressive disease and need treatment immediately. And so, in that situation, you know you may need to consider a different sort of class of agents, potentially something like bendamustine or rituximab elotuzumab, or even, you know, lenalidomide, which are, you know, agents that are frequently utilized in that setting. But, I would particularly in this case use those agents to kind of calm things down and ultimately move the patient into car T-cell therapy, you know, if they're interested and that's felt to be something they could benefit from.

Dr. Caimi:
Yeah, I agree with you. I think, I think probably with the new results of the pilot but one of the remarkable things about car Ts is even though there really been seen as agents that have difficulty being tolerated, they've really made a big impact into the results of patients who, you know, are at more advanced age, who have comorbidities, who before were not eligible for auto transplant, particularly patients over age of 80 who with agents like lenalidomide or kymriah, they're able to tolerate them really well and without any significant adverse events, sometimes treated as an outpatient. I think I agree with you when patients who have a slow course of disease waiting for treatment with car Ts can be done. I think the additional consideration is that if logistics or patient preference don't permit treatment with car Ts, probably the group that benefits most from carfilzomib lenalidomide, those patients who have had a long time to relapse who are receiving this combination on the second line. And I would expect that there is a relatively high chance that the patient could serve, could respond to that and tolerate it well. So that probably would be my specific second choice after, if those are not available probably choose carfilzomib lenalidomide. If the car T path is not going to be followed, the question would be whether what to bridge them with. Like you say, I think regimen would be something reasonable. Whether other chemotherapies would be offered to a patient who's 83 would be, a difficult proposition.

Dr. Riedell:
Absolutely. Yeah, and I think, you know, the other thing to consider is in terms of determining which might be the best option is, one of the things that we do know with car T-cell therapy is that you know, for patients that respond and specifically those that go into a CR that the duration of responses, you know, rather long, and in many instances, we think there is a plateau. So that would certainly be one distinct benefit of car T-cell therapy is that it may be a one and done treatment for this patient versus something like lenalidomide which does require continuous therapy and then the maintenance therapy with, by itself. But again, those are certainly important points to discuss with patients when, you know, determining best options for them in, in the second-line setting.

Dr. Caimi:
Yes, thank you very much. And I think that this is kind of raising the point for older patients. If you, if you confronted a patient in a similar scenario that was younger, probably your choice would be much more heavy on, on considering other alternatives. That scenario, would you consider different approach?

Dr. Riedell:
If they were a younger patient. I think my typical approach would be to try to be a little bit more aggressive. You know, it may not necessarily be a non-car option, but I think that does open up the possibility of if they're an early relapsing patient, using something like would also be an option as it's approved in patients with early relapse in refractory disease. But the patients that were evaluated in the Zuma-7 trial were also transplant candidates. And so that's a little bit different in this case. Lisocabtagene maraleucel is also approved in the second-line setting for patients with early relapse or refractory disease. So, I think in that setting, you could really go either way. I know many of our colleagues are choosing car T-cell products based on patient fitness and patient comorbidities, and, you know younger patients may more apt to receive something like axial, whereas patients with more comorbidities and of the more advanced age, potentially one of the 4-1BB constructs like lyocell or tisa cell.

Dr. Caimi:
Well, thank you very much for these excellent responses. In this case, kind of, we think illustrates the multiple different alternatives that you can have for patients with relapse refractory large cell lymphoma. I thank our audience for their attention and thank you very much.

Dr. Riedell:
Thank you.

Announcer:
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