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Examining the Current Treatment Landscape & Future Horizons in MCL

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

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the current and future treatment landscape for patients with mantle cell lymphoma, or MCL for short, is Dr. Tycel Phillips. Dr. Phillips is an Associate Clinical Professor in the Division of Lymphoma, Department of Hematology, and Hematopoietic Cell Transplantation at City of Hope in Duarte, California. Dr. Phillips, thanks for being here today.

Dr. Phillips:
Thank you for having me.

Dr. Turck:
So let's get right into it, Dr. Phillips. What are the treatment options currently available for MCL?

Dr. Phillips:
So when we think about treatment options for patients with mantle cell lymphoma, it's easiest to break it into the line of therapy, so we have front line or untreated patients. So in that space currently, there is chemoimmunotherapy, and we dichotomize that based on patients' age and fitness currently. So for those who are young and fit and ones we consider to be a candidate for an autologous stem cell transplantation, these patients will typically get a regimen of high-dose intensive chemotherapy, something typically based with cytarabine followed by an autologous stem cell transplantation. And then we would typically follow with three years of maintenance rituximab, given every eight weeks. Maintenance rituximab is utilized in this patient population, given a survival benefit that was shown in a study from France. Obviously, because of the introduction of high-dose therapy, and also the use of autologous stem cell transplantation, these patients are at risk for infection, cytopenias, sometimes requiring blood transfusions. And then there are secondary cancer risks that come from autologous stem cell transplantation and very rarely, marrow failure. For those who are unfit for intensive chemotherapy, it is typically less intensive chemotherapy regimen, such as RCHOP, followed by maintenance rituximab that was indicated to be beneficial from the German Elderly study. Now, rituximab in that situation can be given indefinitely. There did continue to show a progression-free survival benefit. Bendamustine and rituximab was evaluated in two studies. The initial study was the StiL study from Germany. And this was recapitulated here in the United States in another subsequent study comparing bendamustine and rituximab to RCHOP RCVP. Bendamustine and rituximab was found to be a better treatment regimen for patients with mantle cell lymphoma without the incorporation of maintenance therapy. Speaking of maintenance, it was evaluated in another German study, where it was randomized VR with maintenance versus no maintenance, and just indicated that maintenance rituximab was not beneficial in the perspective study. But there are several randomized studies that have shown a benefit of maintenance rituximab and is something that most people incorporate into their clinical practice.

With that being said, the risk of maintenance rituximab, especially after bendamustine, there is an increased risk of infection, especially viral infections due to prolonged lymphopenia and hypogammaglobulinemia. For those who do not want to get chemotherapy, options include utilization of BTK inhibitors. So ibrutinib has been studied in a young, fit patient population and an elderly patient population and the young, fit patient population in the study is part of the WINDOWS-1 study when patients got a year of ibrutinib/rituximab followed by four to eight cycles of R-hyperCVAD. During that year of therapy, patients had very high overall response rates noted with typical adverse events that we noted with ibrutinib and other BTK inhibitors, such as diarrhea. We saw arthralgias, myalgias, rash, infection, especially upper respiratory infections, and there is a risk of bleeding noted with this and cardiac toxicity. Thereafter, we did have the

ibrutinib/rituximab elderly study, also from MD Anderson which looked at 30 plus patients. In this situation, while the overall response rate was very high, patients had a high rate of discontinuation due to inability to tolerate ibrutinib, which was given indefinitely in that study.

In the second line setting, we have the BTK inhibitors. We have ibrutinib, acalabrutinib, and zanubrutinib. For the most part, the second-generation drugs were evaluated, hoping for an improved safety due to more fidelity to the BTK receptor. As time has moved on, while overall response rate between all three drugs are about the same, it does appear that there is maybe some similarity between a side effect profile between ibrutinib, acalabrutinib, and zanubrutinib, but we need further time to really tease that out. And in the third line setting, we have brexucabtagene autoleucel, which is a CAR T product, which has shown to be very effective in respect of any sort of patient characteristics in relapsed, refractory setting, albeit as time has gone on, we still have continued relapses on this therapy, so we don't know its true duration of response. And also with this treatment is sort of belabored by a typical T-cell directed therapy side effects, such as cytokine release syndrome and neurotoxicity, which can be very severe in certain select patients.

Dr. Turck:
Now with all that in mind, what are some of the most common challenges you run into when using these treatment options?

Dr. Phillips:
So in the front-line setting, I think the biggest challenges that we run into are P53 mutated mantle cell lymphoma patients who just don't know the best way to treat these patients, and none of the treatments I mentioned thus far seem to make a difference. Then a second line setting, the biggest concern we have as of right now, there's the side effect profile of the BTK inhibitors and whether we can successfully combine these drugs with anything else and hopefully improve the progression-free survival and not necessarily add any significant amount of toxicities. Then in third line setting, I think we've already discussed the challenges with CRS and brexucabtagene, so the question is whether any of the newer CAR T products, such as Liso-Cel, may get any indication to have a better safety profile or whether it's better to use other alternative ways of harnessing T-cell therapy versus CAR T, and maybe that includes using some of these bispecific antibodies, which are like an off-the-shelf CAR T product. Thereafter, what do we do for patients who fail CAR T? It is a bit of a question mark, as we don't have any FDA-approved options other than older options, which were approved before the BTK inhibitors, such as bortezomib and lenalidomide, which thus far have not proven to be very effective. Or obviously, we can continue giving more chemotherapy, but sometimes these patients are very beat up after the treatments we've given already and may not be fit for a chemotherapeutic option any longer.

Dr. Turck:
For those just tuning in, you're listening *to Project Oncology* on ReachMD. I'm Dr. Charles Turck. I'm speaking with Dr. Tycel Phillips about current treatment approaches for patients with mantle cell lymphoma, or MCL.

So given those challenges associated with current treatment options, Dr. Phillips, let's look to the future. Would you tell us about new therapies in development for MCL?

Dr. Phillips:
Sure. Some newer treatments that are in development for mantle cell lymphoma include the noncovalent BTK inhibitor, pirtobrutinib, noncovalent being that it doesn't permanently bond to the bonding site and sort of releases and reattaches, releases, reattaches. This agent was shown to be effective in keeping patients who had progressed on prior covalent BTK inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, and it's currently being evaluated in a phase 3 study comparing its efficacy to these three drugs in a second line setting. There are also the CD20/CD3 bispecific antibodies, which are very similar to what we see with CAR T. These agents are off-the-shelf products, since they are just antibodies and don't need to be manufactured. So looking forward, we'll see how the efficacy and safety of these sort of treatments compare to CAR T and whether this is something that can be integrated into the community a bit easier than what we have so far with CAR T products. There are also ROR-1 antibodies, as ROR-1 is a very frequently noted target in mantle cell lymphoma. So there's a naked antibody, zilovertamab, which has been studied as a single agent and in combination with abrutinib, and there is also zilovertamab vedotin, which recently presented single agent data and showed some efficacy in the post-BTK setting, which is also being evaluated further as a single agent and in combination.

Dr. Turck:
And what are some other key considerations clinicians should keep in mind about these potential treatment options?

Dr. Phillips:
I think the biggest to consider is sequencing. With pirtobrutinib, we know it works post-covalent BTK inhibitor. We don't know the reverse, so we don't know that the covalent drugs work after pirtobrutinib. Then part of the issue also is that the reason for BTK failure in a mantle cell lymphoma patient is not well understood, so we don't necessarily know why these drugs stop working, which conversely

means we don't necessarily know why pirtobrutinib works in this patient population.

Then when it comes to bispecifics with these run alone CAR T, will they be before CAR T, will they work after CAR T? I think these are things that need to be sorted out, and we just don't have clear enough information to make that decision. And for the other drugs that we mentioned, will they be able to slide into the no man's land that we call fourth line setting at this point? Will they be responsive in patients who failed BTK inhibitors, failed CAR T, and failed bispecifics? Will they be able to salvage these patients, so we can get more extended remission in this patient population?

Dr. Turck:
As we close our discussion today, Dr. Phillips, are there any final thoughts or takeaways you'd like to leave with our audience?

Dr. Phillips:
I think the biggest takeaway is that we've continued to make improvements in the care of patients with mantle cell lymphoma. I think the future looks bright, and I think at some point, we'll get to the situation where if we can't necessarily cure this cancer, we will make it a more chronic disease, more akin to what we see with chronic lymphocytic leukemia, and extend the amount of time that these patients can live with their cancer, and hopefully have a better quality of life as we get more and more of these specified and targeted treatments that have less off-treatment side effects. So I think the future's bright, as I said. I think moving forward, some complicating factor that we'll have to figure out, obviously we're in a COVID era, and that does impact a fair number of the treatments that we give for these patients, so how to comanage that, and also necessarily give these patients the most efficacious therapy will be something that we'll figure out as time will go on. But I am excited to see what the next couple years bring to this patient population.

Dr. Turck:
Well as those takeaways bring us to the end of today's program, I want to thank my guest, Dr. Tycel Phillips, for joining me to discuss current treatment options and share insights on new therapies in the works for patients with MCL. Dr. Phillips, it was great speaking with you.

Dr. Phillips:
Thank you for having me. I enjoyed the conversation.

Announcer:
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