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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Managing MCL After BTKi Failure: The Expanding Role of CAR T-Cell Therapy

Announcer:
You're listening to *Project Oncology* on ReachMD, and 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. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss evidence-based strategies for managing relapsed/refractory mantle cell lymphoma after BTK inhibitor therapy is Dr. Michael Wang. He's a Professor in the Department of Lymphoma and Myeloma in the Department of Stem Cell Transplantation at MD Anderson Cancer Center in Houston, Texas. Dr. Wang, thanks for being here today.

Dr. Wang:
It's my pleasure to join the audience and you on this program.

Dr. Turck:
Well, we look forward to a great discussion. Why don't we start with some background, Dr. Wang. Would you tell us about the clinical implications of BTK inhibitor failure in mantle cell lymphoma and what the therapeutic landscape currently looks like for these patients?

Dr. Wang:
Mantle cell lymphoma used to be the worst lymphoma to treat among all the lymphomas. But in 2013, the FDA approved a drug called ibrutinib. It is the first-generation covalent BTK inhibitor. The second one was the second-generation BTK covalent inhibitor called acalabrutinib, which was approved in the US in 2017. Then, there was another drug from China called zanubrutinib. It was approved in 2019 for the treatment of relapsed mantle cell lymphoma. And all of a sudden, we had three BTK inhibitors, and we've treated many patients. We have saved patient lives; we kill the tumors. However, those three targeted therapies are not curable. We also found that if the patient's lymphoma is resistant to prior BTK inhibitors, then the patient doesn't live very long—about less than a year, especially in the aggressive cases.

Then, the next breakthrough was CAR T-cell therapy. And nowadays, we are moving toward more immunotherapies, such as CAR T-cells against novel targets and also bispecific antibodies. So far, there's mosunetuzumab; there's CD20/CD3, and glofitamab; there's CD20/CD3, and epcoritamab. CD20 and CD3 are used subcutaneously. That is the current status of mantle cell lymphoma.

Dr. Turck:
Now, guideline-based strategies often suggest lenalidomide with or without anti-CD20 antibodies as a chemotherapy-free option. In your experience, what role do these immunomodulatory drug or IMiD-based regimens play in the post-BTK inhibitor setting?

Dr. Wang:
Lenalidomide is very different from chemotherapy. Especially, it is very different from the BTK inhibitors because it works as a cereblon-binding agent, and it works by modulating the immune host. So its mechanism of action is completely different from BTK inhibitors. If you use the single agent, the effect is not that good, but if you use the combination, it is especially effective. Even if the BTK does not work, lenalidomide plus rituximab could still put the patient in remission.

Dr. Turck:
So then given all of these options, Dr. Wang, how do you approach treatment selection and sequencing for patients who fail BTK

inhibitor therapy? And are there any clinical or biologic factors that tip the scale towards IMID-based therapy versus CAR T-cell therapy?

Dr. Wang:
The IMID-based therapy has the strength because lenalidomide is an oral drug and rituximab is given by a peripheral catheter, so it's a very easy regimen to give. However, lenalidomide has found to cause cytopenias, especially neutropenia and thrombocytopenia. Furthermore, in randomized clinical trials within myeloma, it can also cause secondary malignancies. Therefore, in lymphoma, we use about 6 to 8 cycles. We rarely use it beyond a year.

So with this information, if, for example, the patient has used BTK inhibitors, I can use lenalidomide plus rituximab with or without venetoclax. Venetoclax is a BCL-2 inhibitor agent to overcome resistance. We can use that. I can also use CAR T to overcome BTK resistance.

BTK inhibitor resistance is mainly divided into two categories. One category is that although they relapse after the BTK, the tumors are very small, and there are no high-risk features. This way, if we use our tool, it should be very effective. And if we want to add on venetoclax, the second oral agent, the trial has already proved that is also effective.

But after the BTK resistance, BTK inhibitors can cause relapse with high-risk disease: P53 mutation, blastoid or pleomorphic morphology variant, and the ki-67 proliferation index over 50. Those are very aggressive tumors. You do not use targeted agents or three-drug combinations. You use CAR T-cell therapy because for those high-risk patients, if you use targeted combinations, it won't last very long, and it makes the resistance even worse.

So CAR T-cell therapy is used to combat the high-risk features or high tumor volumes after BTK inhibitor. And the targeted combination is used in low-risk tumor relapse after BTK with low tumor burden and low risk factors.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking to Dr. Michael Wang about managing relapsed/refractory mantle cell lymphoma after BTK inhibitor therapy.

Now, Dr. Wang, if we zero in on CAR T-cell therapy for just a moment, we know that timely referral can be crucial. But unfortunately, it's not always straightforward. So with that being said, what are some best practices for preparing eligible patients for cellular therapy, especially in terms of workup and bridging?

Dr. Wang:
First of all, any mantle cell lymphoma patient deserves an academic visit. That visit should be as early as possible. But also, it is impossible to prevent doctors from treating the mantle cell lymphoma in the first-line or the second-line, but if it's after the second-line therapy and the patient is not doing well, refer to an academic center as soon as possible to consider CAR T-cell therapy. I think after first- or second-line will be the best timing.

If you refer earlier, that's OK, too. Nowadays, the referral patterns are no longer just from the community doctors. Patients refer themselves all the time, even more than the referred one. That is good. But oftentimes, the patients self-refer too late, but even if it's too late, it's still better than nothing, right? So send the CAR T-cell patient as early as possible. Well, at least after the second-line failures, you need to refer them.

All of the studies indicate that the pre-infusion tumor volume affects the side effects, the degree of side effects, the efficacy, and the response rate. So if you think about it, let's say you have a 10-centimeter tumor, and you don't do anything about it. You've given them the CAR T-cell. The CAR T-cell probably can only cause a partial remission because it cannot penetrate the center of the tumor mass, and it's probably caused a lot of side effects like CRS or ICANS. But let's say you actually were able to use HyperCy-Dex, dexamethasone, rituximab, and cross-radiation to reduce the tumor to 4 centimeters; the CAR T-cell can then eradicate that tumor to 0. So that would be a great strategy. So treatment bridging therapy is vital for the success and safety of the patient.

Dr. Turck:
Now, as with any treatment approach, immune-based therapies have some important safety considerations. Fortunately, the ASTCT provides grading guidance for adverse events that you had mentioned before, like CRS and ICANS, and the NCCN toxicity protocols can assist with steroid dosing, anti-IL-6 strategies, and even decisions around ICU escalations. So how can these frameworks help clinicians manage risk and how can teams best implement them?

Dr. Wang:
Sometimes, there are many rules, but the fundamental rule is basically, when to use the steroids, when to use tocilizumab, when to use highest-dose steroid, and when to escalate to an even higher dose of that steroid. I think in our institution, there is so much exposure that you can hardly forget the rules. But in mantle cell lymphoma, oftentimes, you need the time to accumulate the experience. And after

you manage some cases, that becomes second nature.

Dr. Turck:
Well, we've certainly covered a lot of ground today, but if we look ahead before we close, Dr. Wang, how do you see the roles of IMID-based therapy, bispecific antibodies, and CAR T therapy evolving for relapsed/refractory mantle cell lymphoma? And what's still needed to further optimize access and outcomes?

Dr. Wang:
A lot of people say, “Dr. Wang, everybody says mantle cell is not curable. What do you think?” I think that mantle cell lymphoma is no longer not curable. We are in the process of curing some mantle cell lymphoma patients. So what's the definition of cure? My personal bias after I consulted many people with much literature is that if the patient has achieved a complete remission for 15 years without interruption, those patients are cured. So in my clinic, I have many patients who have CRs for more than 15 years, and I send them to a survival clinic. I regard them to be cured. My feeling is that we are in the process of curing many mantle cell lymphoma patients.

In the future, even with the bispecific antibodies, that’s not enough because patients still relapse. We are going to be working with new and fast CAR Ts with different targets and bispecific antibodies with combinations and different targets. And we also need to work on the biological basic translational research.

Dr. Turck:
Well, with those forward-looking comments in mind, I want to thank my guest, Dr. Michael Wang, for joining me to share these key strategies for managing relapsed/refractory mantle cell lymphoma after BTK inhibitor therapy. Dr. Wang, was great having you on the program.

Dr. Wang:
Thank you.

Announcer:
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