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### Applying Data to Patient Care: Case Review in Follicular Lymphoma

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Applying Data to Patient Care: Case Review in Follicular Lymphoma" is provided by Prova Education.

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Dr. Nastoupil:

Recent clinical trial evidence supports the use of available and emerging options in relapsing refractory follicular lymphoma. How can we use this information to optimize treatment approaches and improve outcomes for our patients?

This is CME on ReachMD, and I'm Dr. Loretta Nastoupil.

Dr. Leonard:

And I'm Dr. John Leonard.

Dr. Nastoupil:

So let's get started. Dr. Leonard, can you give us a brief introduction into EZH2 mutations in follicular lymphoma and the importance of testing?

Dr. Leonard:

Certainly. So EZH2 is really in the category of epigenetic modifiers. There are a number of different chromatin writers, erasers, and readers in chromatin in tumor cells, as well as in normal cells. And one of those is EZH2 in the category of writers. These are enzymes that modify histones and therefore have modifications on DNA. So EZH2 can be active through a variety of different mechanisms, but one mechanism is through gain of function mutations in EZH2. So in certain types of tumors, there are mutations of EZH2, which lead to gain of function. And in follicular lymphoma in particular, our topic today, these seem to occur somewhere around 20% of patients or samples of follicular lymphoma.

So what happens is that these activating mutations can lead to, really, changes in the methylation state of histones. This affects the way that the chromatin is condensed. And this leads to a variety of different changes in transcription of a variety of different tumor suppressor genes. So by inhibiting EZH2, particularly in the cases where there are EZH2 mutations, by inhibiting EZH2, this leads to a therapeutic target because of its effects on tumor suppressor gene and having antitumor effects. Mutations of EZH2 are relevant for follicular lymphoma, in particular. They're also potentially relevant in germinal center diffuse large B cell lymphoma and other types of cancer as well, where these mechanisms are operative.

Dr. Nastoupil:

That was a very nice summary of the role of EZH2, both the lymphoma biology as well as the potential microenvironment, setting the stage for how we might therapeutically manipulate that.

So let's go through a case and see if we can put some of the recent evidence into clinical practice.

A 67-year-old woman is referred for recurrent follicular lymphoma. At age 62, approximately 5 years ago, she developed symptomatic, diffuse, bulky adenopathy and was found to have follicular lymphoma, grade 1. She was treated with bendamustine and rituximab and achieved a complete response. After careful consideration of the risks and benefits, she decides against maintenance therapy and is observed. Three years later, at age 65, she again develops symptomatic progression. A biopsy confirms follicular lymphoma, grade 2. She received lenalidomide and rituximab over one year with a good partial response and resolution of her symptoms. And now a year later, at age 67, she herself notes an enlarged lymph node suggestive of progression of her disease. Physical exam reveals 2.0 cm bilateral cervical adenopathy and a 3.0 cm unilateral inguinal lymph node. PET CT confirms the enlarged lymph nodes noted on physical exam. In addition, mild splenomegaly, and 1.5 cm mediastinal and 3.0 cm abdominal lymph nodes are also revealed. The maximum SUV is 9.3. Laboratory data reveal a hemoglobin of 11.4. Platelet count of 141,000 and LDH or serum lactate dehydrogenase is within the normal limits. Again, a biopsy is pursued revealing follicular lymphoma, grade 1. Mutational profiling is sent, and she is noted to have an EZH2 mutation. She feels well, but the cervical lymph nodes bother her cosmetically and remind her of her diagnosis.

So Dr. Leonard, can you discuss her potential management approaches?

Dr. Leonard:

So this is an interesting case that really fits a, I would say, reasonable pattern for follicular lymphoma. This is a patient who presents at a fairly typical age, just over 60 at her initial diagnosis. And she was treated with bendamustine/rituximab, and I would say that that is a standard regimen for follicular lymphoma. And she had a good response. So her long-term outlook is good in that she had a 5-year remission. So she does not fall into that POD24 group where early progressors with follicular lymphoma have a less favorable prognosis. She relapsed at age 65 and receives another reasonable treatment approach, lenalidomide and rituximab, and this was informed by the AUGMENT study that showed a benefit of adding lenalidomide to rituximab.

And so now, this is a patient who has, now approaching her third-line therapy, she's relapsed again. She has non-bulky disease, but she does have some indications for therapy. She's anemic, and she has some cosmetic issues that certainly are disrupting her life to some extent. And so it certainly is reasonable to give this patient some treatment. But it also is reasonable to try to balance out the risk/benefit profile and giving this patient, whose main indication for therapy is really cosmetic, I would say, in some ways is not something that is going to drive a very aggressive chemotherapy-based approach in my estimation.

So this is a patient who needs treatment; like any patient with follicular lymphoma, you need to consider the issue of does the patient have transformation? And our job is a little bit easier here in this case in that her LDH is normal; her SUV on her PET scan is relatively low. These items argue for the lack of transformation. It doesn't prove that she doesn't have transformed disease, but we now know she has a biopsy that shows no transformation. So we've done a pretty good job, I would say, in ruling that out.

It would be reasonable to think about a PI3 kinase inhibitor in this type of patient. We have several of them that are available and approved. Some oral, one intravenous. These have about a 50% response rate; they are mostly partial responses. The durability tends to be in the range of a year. This would be a reasonable option. I would say that the challenge of the PI3 kinase inhibitor in some cases is toxicity. You're thinking about an intravenous, almost weekly drug or a drug that has some risk of hepatic side effects, autoimmune toxicities, and infections that are not insurmountable, not unmanageable, but certainly perhaps affect the risk/benefit analysis, here.

Additionally, one could use a chemotherapy-based approach such as R-CHOP or following that up with more aggressive treatment or autologous stem cell transplant. I am not sure that I would be approaching a patient like this with such an aggressive strategy, given that her symptoms are pretty mild. She has low bulk of disease. I think I would be looking for a less aggressive approach to her treatment.

We also have new data with CAR T-cell therapy suggesting that some patients, the majority of patients with follicular lymphoma in the relapse setting can respond. And these may be durable, although we have limited follow-up with respect to the number of years of duration. I think for a patient like this, that's a pretty involved therapy. It would fall into a more aggressive approach that I would be less inclined to take with this patient, but perhaps in the future.

So I think tazemetostat would be a very reasonable option for this patient. It's an oral therapy. It's generally pretty well tolerated. Main side effects are some fatigue, some mild GI toxicity in some cases, but in general, I would expect her to tolerate it well. It would probably fit the profile of a drug that would be attractive to a patient like this. And also, we know that she has an EZH2 mutation, and that suggests a higher response rate to tazemetostat. And so I think, in my mind, that would probably be the preferred approach, given that it is likely to work, especially given the presence of an EZH2 mutation. And something that is probably going to be pretty manageable for her as far as convenience and side effects and accomplish her treatment goals.

Dr. Nastoupil:

That's a very nice overview of the many options patients have available to them.

So let me ask you this question: What if she had an EZH2 wild-type situation? How would that then change your recommendation or

your consideration amongst the available options?

Dr. Leonard:

So the data we have around EZH2 mutations in recurrent follicular lymphoma are that in the ballpark of about 70% or so of patients respond if they have any EZH2 mutation. And that falls, although is meaningful, I would say, to about 35% in patients that have the wild-type.

So if this patient had wild-type disease, she would still have a pretty meaningful response rate to tazemetostat, again in the 30% to 35% response rate. And given that she is well and has a low tumor burden disease, it would seem to me like that would be a reasonable approach, perhaps, based a little bit more on the toxicity profile on the preferences that might be relevant to this patient. So I do think for some patients, particularly those where quality of life and ease of administration and bulk of disease suggests that a less aggressive approach may be reasonable, in that scenario, even treating that patient with tazemetostat, even if she had wild-type disease, would be a reasonable consideration that should be considered amongst the other options.

Dr. Nastoupil:

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Loretta Nastoupil, and here with me today is Dr. John Leonard. We're discussing strategies to optimize therapy outcomes for patients with EZH2 mutations and relapsing refractory follicular lymphoma.

So I thought that was an excellent case discussion. When treating patients with follicular lymphoma, we're concerned about possible treatment-related adverse events, particularly given the prolonged natural history of the disease. Dr. Leonard, can you please discuss some of those possibilities and provide a few strategies to minimize risk?

Dr. Leonard:

Certainly. So the main side effects that we see with tazemetostat in follicular lymphoma come from a study of about a hundred patients that received tazemetostat for recurrent follicular lymphoma at the recommended dosing schedule. And I would say that it's important to keep in mind that toxicities are principally grade 1 and 2 in nature. There are relatively infrequent grade 3 or 4 toxicities. So that obviously is an important consideration. The toxicities that occurred in the key clinical trials included, I would say, mild cytopenias, and there are some dose modifications if those occur, but those tended to be mild. There is some fatigue. There was some GI toxicity, and I would say that that's probably the most prominent toxicity, somewhere around 20% to 25% of patients have some element of GI side effects; these are again grade 1 and 2 in nature, primarily. Occasional rashes were seen, somewhere around 10% to 15% of patients. And then of course, one can see infectious complications in this population, which can be due to the underlying disease, prior therapy, and as well as a contribution of the drug.

I would say that in this patient, you know, the management of side effects typically are through dose modifications and/or symptomatic or supportive care. Again, these tend to be pretty mild, grade 1 and 2. And I would also say that compared to some of the alternatives that we discussed earlier, these would generally be, I would say, preferable and pretty manageable in the context of chemotherapy and some of the alternate treatments that one might consider for a patient of this type.

Dr. Nastoupil:

Yeah, and as you mentioned, given that most were grade 1 or 2, there were very low rates of either drug interruption, dose reduction, and I agree that it compares quite favorably to the other options available in this third-line or later setting.

Well, this certainly has been a fascinating conversation, but before we wrap up, Dr. Leonard, do you have one take-home message that you want to be sure our audience really heard?

Dr. Leonard:

I think in treating patients with follicular lymphoma, since the majority of patients are going to die with their disease, not from their disease, and this is an example of a patient who one could reasonably predict that, that really assessing quality of life, the risk/benefits of treatment, and the goals of therapy are really essential in choosing the appropriate treatment option for an individual setting.

Dr. Nastoupil:

As you've heard today, there are a number of effective strategies for patients with relapse follicular lymphoma. I fully recognize that there's significant heterogeneity in terms of patient-specific characteristics, but it's important to keep in mind the goals of our therapy, which is to extend life, but also to have a positive or the lack of a negative impact on quality of life. So consideration of efficacy and safety profiles is particularly important in follicular lymphoma.

So unfortunately, that's all the time we have today. I want to thank our audience for listening in and thank you, Dr. Leonard, for joining me and for sharing all of your valuable insights. It was great speaking with you, today.

Dr. Leonard:

Thanks very much. It's been great to be with you.

Announcer:

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