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Creating Personalized Care in Relapsed/Refractory Follicular Lymphoma

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Dr. Nastoupil:
The epigenetic modulator EZH2 is known to play a crucial role in mediating the lymphomagenesis of follicular lymphoma [FL]. In the relapsing refractory disease setting, inhibition of EZH2 has shown efficacy. Are you confident about using molecular testing to guide therapeutic decisions in follicular lymphoma?

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

Dr. Matasar:
And I’m Dr. Matthew Matasar.

Dr. Nastoupil:
Let’s get started. Dr. Matasar, can you tell us about the role of EZH2 in the pathobiology of follicular lymphoma and the importance of testing for this mutation?

Dr. Matasar:
Ha, I can try. So it’s been known now for, you know, going on 2 decades that this gene, EZH2, is critically and centrally involved with maintaining the germinal center. This essence of lymphoid tissues, where B cells go to grow up and to fight antigens and then to mature into either memory cells or plasma cells and to go off and do their work.

So, EZH2’s been long recognized as one of these key gatekeeper genes, but its role in lymphomagenesis, particular for follicular lymphoma as well as for germinal center large B cell lymphoma, is only more recently understood. And we now know that there’s a subset of patients with follicular lymphoma who harbor activating mutations in this gene, EZH2. And what that leads to is cells that should be entering the germinal center, proliferating, dividing, and then stopping that proliferation and maturing and going off, stuck in that germinal center mode, where they just keep proliferating as if they’re trying to be trained, but they get stuck in that mode. And this, we believe, can then lead to clonal development of low-grade follicular lymphoma.

We know that these mutations are present in about 20% of low-grade FL, although, truthfully, EZH2 is probably deranged in a larger fraction than that, whether it’s gaining copy number or alterations in other pathways that feed back into the EZH2 pathway, leading to either direct or indirect activation of this in maybe as many as half of patients with follicular lymphoma.

Dr. Nastoupil:
So, Dr. Matasar, that’s a nice illustration of the importance of EZH2 in the role of lymphomagenesis. Do you think this is an early event?

Dr. Matasar:
It's very clearly an early event. You can see it even in follicular lymphoma in situ, in premalignant conditions, or early on, and it's sustained in patients. If we do serial biopsies, this mutation is really carried through the patient's journey with follicular lymphoma.

Dr. Nastoupil:
And so now, are you suggesting that this be something that's routinely tested for among patients with follicular lymphoma?

Dr. Matasar:
So I'd say, right now, given that we have the availability of a commercially available EZH2 inhibitor in the form of tazemetostat, that it's relevant for us in routine clinical practice to test for the presence of an activating EZH2 mutation so that if and when the time comes that you would be entertaining using tazemetostat, that you can make that decision with your patient informed by your understanding of the patient's mutational status.

Dr. Nastoupil:
Putting this to practice, keeping this overview of EZH2 mutations in mind, Dr. Matasar, what are some of the different settings of follicular lymphoma treatment where we would potentially be able to target these mutations?

Dr. Matasar:
That's a great question. So, I guess I would break it down into what we can do right now in the clinic, and then we can think about what are we trying to accomplish as we go forward with targeting this important aspect of lymphoma biology.

So right now in clinical practice, we have tazemetostat, and it has an FDA-approved label in 2 different clinical settings. The first is in patients who've had 2 or more prior lines of therapy and whose disease does indeed harbor an activating mutation of EZH2. And then the second population is patients who have relapsed/refractory follicular lymphoma with any number of prior lines of therapy and regardless of their mutational status, if that patient really doesn't have any other safe and appropriate therapeutic options available to them. So that's where we are right now with targeting EZH2 in the clinic.

In the future, I think that there's a lot of opportunities to further target this part of lymphoma biology. And because EZH2 mutation is an early event, you could really think about how best to incorporate targeting EZH2 in any line of therapy—from first-line therapy observable patients, you know, think about a preemptive strategy targeting EZH2, all the way down to transformed multi-relapse post-CAR T, the most dangerous of follicular lymphoma patients. There's really no point in that patient journey that one couldn't think about how best to deploy an EZH2 inhibitor in service of the patient.

Dr. Nastoupil:
You bring up a great point, particularly given the favorable safety profile. Where do you think this currently fits in, particularly for those patients who have an EZH2 mutation, among the treatment landscape?

Dr. Matasar:
So for the patients that have an EZH2 mutation, we have very clear evidence about tazemetostat's activity with an overall response rate in the pivotal study that led to its approval of approximately 70% and progression-free survival approaching a year with an agent that has an extraordinarily favorable toxicity profile with, you know, fewer than 10% of patients coming off of study due to adverse events, very, very little grade 3+ toxicity, period. You have this very nice balance of an agent that has a very high overall response rate and an excellent toxicity profile. The durability of the response is imperfect, and I think that it tells us that as monotherapy, although very active, that perhaps this drug, given its activity and safety, may best be developed in combination with rational partners to try to come up with a new comprehensive multi-agent program really targeting underlying lymphoma biology.

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. Matt Matasar. We're going to dive a little bit deeper into the role of EZH2 in lymphomagenesis of follicular lymphoma, the importance of testing for mutations in EZH2 in follicular lymphoma, and talk about the efficacy and safety of targeted agents, specifically tazemetostat.

So, Dr. Matasar, you did a nice overview of some of the potential advantages of tazemetostat, particularly in EZH2-mutant follicular lymphoma. What are your thoughts about it in regards to EZH2 wild-type? Again, highlighting some of the safety and efficacy.

Dr. Matasar:
Right, so you know this area of clinical investigation was really driven by the recognition of this EZH2-activating mutation, which is really, kind of, only happens in follicular lymphoma and germinal center large B cell lymphoma. This isn't a mutation that is seen in other types of cancer, which is interesting and really hasn't been fully explained. Nonetheless, we do see that this agent does have activity even in follicular lymphoma cases that do not have an activating mutation. And we could say, "Well, we understand that EZH2 is really integral to

germinal centerness," so at some sort of basic level, it makes sense that targeting germinal centerness should indeed help treat follicular lymphoma, which is the paradigmatic germinal center disease. But the science of it really hasn't been fully worked out, at least to my satisfaction.

But we know that EZH2 inhibitors do a few different things. Number one, there clearly is some modification of the microenvironment, and EZH clearly isn't just about histone satellation and turning on and off these germinal centered genes; there's clearly more to it than that. There's microenvironment interactions, there's cross talk to other important pathways like MIC, so it may be that it's these other pleotropic effects of EZH2 inhibition that is driving the response in those patients. Or maybe that we just don't fully understand what it means to be EZH2-activated, and it's patients who may have an increased copy number of EZH. There's no mutation, but there's a functional activation of the gene through direct or indirect mechanisms that we're targeting.

We don't have a great predictive model yet for which patients with EZH2 wild-type respond. We know it's a smaller fraction of patients in follicular lymphoma; it's probably about 1 in 3 that will respond. But those patients that respond, their median progression-free survival is actually better, on average, than the mutant patients who respond. So there's something going on there that we, as a scientific community, have yet to fully unravel, but it's important to understand that even some wild-type patients can derive significant clinical benefit from EZH2 inhibition.

Dr. Nastoupil:
There are also ongoing trials for combination therapies. Dr. Matasar, can you give us some insight on those combinations and where they might fit into clinical practice?

Dr. Matasar:
Right, so the combined ability of tazemetostat, given its excellent safety profile, certainly leads people like you and me, Dr. Nastoupil, to think, "Well, what can we pair this with that would be biologically rational and could offer some measure of synergy?" And that work is definitely ongoing. And there's already been early-phase clinical trials that have been reported out combining tazemetostat with chemo-immunotherapy like good old R-CHOP. I think that study that's been reported, that's actually in DLBCL, not follicular lymphoma, but the principle is the same, where you could see if adding this agent onto a chemoimmunotherapy backbone could improve outcomes. That would be in newly diagnosed patients in whom you might be giving R-CHOP or BR as your standard treatment.

In the second-line setting, there's a very important study that has now been initiated and accrual is ongoing, trying to look at what we call the R-squared (R^2) regimen, rituximab and lenalidomide program that's been developed under your watch there, to a great degree. And to see, well, this program has been shown to be very safe and effective in patients with relapse or refractory follicular lymphoma; maybe we can add tazemetostat on to that and further improve outcomes in that patient population.

And then in the multi-relapse/refractory setting, given that we know one of the effects of EZH2 inhibition is a promotion of apoptosis, something that is really halted when EZH2 is constitutively activated. What about pairing it with other anti-apoptotic agents? So there's evidence in the laboratory, at least, that combining tazemetostat with venetoclax, a BCL-2 inhibitor, that there's biological synergy and in vitro synergy. And the question is whether that could translate to improved clinical outcomes with venetoclax, which although follicular lymphoma is the quintessential BCL-2-positive disease, venetoclax monotherapy has been clinically disappointing in the treatment of this. But there's an opportunity here in pairing it with EZH2 inhibition to see whether that combination could offer significant clinical benefit.

Dr. Nastoupil:
I think you raised some really good points, particularly as we learn more about the biology of these germinal center lymphoma subtypes. The treatment landscape, though, in follicular lymphoma is pretty crowded, and I've heard argument made that there's quite good therapies available to these patients, and there's even more questions than answers in regards to how do we sequence therapies. So I'm going to ask you maybe a challenging question: Do you foresee that these combination strategies will surpass the monotherapy? Will it provide any additional information in terms of patient selection? Can you look in your crystal ball and predict what we're going to be doing in the next 5 years?

Dr. Matasar:
You're right. And in some ways, you know, we tell ourselves this is a lovely problem to have, right? The embarrassment of riches that is drug development and drug discovery in follicular lymphoma. And yet this is still an illness that is a life-threatening diagnosis, and we know that when patients have relapsed follicular lymphoma, each time you need to give them treatment, on average, the likelihood of your next treatment working goes down, the duration of remission tends to go down, and the disease becomes more and more threatening with each time up to bat.

We, as a discipline, have had tremendous success in moving away from chemotherapy and at that same time, moving towards targeted

and personalized medicine in this disease. I think that EZH2 inhibitors, tazemetostat as the first example in the class, really give us a chance to further develop our ability to offer personalized individualized care, where we can think about constructing a 3-, 5-, 10-, 20-year plan for a patient, thinking through the sequencing challenges of how am I going to get a patient from age 60 to age 90 successfully and safely, minimizing the toxicities of treatment, minimizing risk along the way, and taking into account their disease's unique individual biological signature.

So, yes, I think there's a real opportunity to use these agents either as monotherapy or in combination and in sequence. And the questions that we need to be asking in these studies are do you see clinical synergy with combination therapy? Or are you better off, as one of my colleagues calls it, with serial monogamy, where you use a single agent and then a single agent and then a single agent to really protract out the clinical course of care? These are important questions, but we have the right studies that we're opening and designing to answer that for ourselves and for our patients.

Dr. Nastoupil:
Well, this has certainly been a fascinating conversation, but before we wrap up, Dr. Matasar, can you share your one take-home message with our audience?

Dr. Matasar:
I think my take-home is that we see now that EZH2 inhibition represents a promising therapeutic option for patients in the present with the availability of tazemetostat for either mutant patients or for frail patients regardless of mutational status. And there's a real opportunity to further develop EZH2 inhibitors as part of a comprehensive and biologically thoughtful approach to a chemotherapy-free life for follicular lymphoma patients.

Dr. Nastoupil:
Well, I sure appreciate your insight and knowledge regarding, again, our current understanding of the biology of follicular lymphoma, where EZH2 mutation has a role in targeting it in terms of drugs like tazemetostat have transitioned successfully into the clinic, but I'm also encouraged and looking forward to the next iterations of studies that may further enhance this targeted approach for patients with follicular lymphoma.

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

Dr. Matasar:
Thank you so much, Dr. Nastoupil. It's been a pleasure.

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