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Critical Review of Data in Follicular Lymphoma

Announcer:
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Dr. Nastoupil:
Follicular lymphoma is an incurable neoplasm that is frequently associated with relapse or refractory disease. Are you up to date on the emerging pipeline and recent data from clinical trials?

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

Dr. Salles:
And I am Dr. Gilles Salles.

Dr. Nastoupil:
So let’s dive right in. Dr. Salle, can you give us a brief overview of our options today for relapse/refractory follicular lymphoma?

Dr. Salles:
Yes. Thank you. I think we have had, in recent years, multiple agents and multiple opportunities to treat our patients. Obviously, chemo-immunotherapy is still on board, even in second line, and obinutuzumab is an agent that has been approved in combination with bendamustine in this setting. Although, when it’s used in first line, that may not be the best opportunity.

Sequentially, a couple of other agents were approved, such as radioimmunotherapy with ibritumomab tiuxetan which is not anymore very much used. PI3 kinase inhibitors, whether they are oral agents such as idelalisib, duvelisib, or more recently umbralisib, as well as agents administered intravenously such as copanlisib, offering different opportunities to manage these patients.

Lenalidomide is an agent that can be combined with rituximab based on the mode of action of the 2 drugs and it has been shown that this combination, so-called the R^2 combination, was effective in patients with relapse and refractory follicular lymphoma. And finally, recently, we had the approval of the first-in-class EZH2 inhibitor called tazemetostat, which is an oral agent that can be administered to patients.

I should also add to this list that, recently axicabtagene ciloleucel was approved in the relapse setting for patients with follicular lymphoma. So we clearly have a broad spectrum of agents, whether they are oral, IV, whether they are single agent or combined, with different efficacy and safety profiles.

Dr. Nastoupil:
That’s a very lengthy list. I think that’s probably good news for patients. But how would the treating physician distinguish between those options? Can you take us into the current safety and efficacy profiles that may help inform treatment selection, given there are so many options in the relapse setting?

Dr. Salles:
Yes, there are clearly different options. We all know the toxicity of chemotherapy, and patients usually would like to stay away from this toxicity, especially in the second line if they have already received such a combination. So oral agents, given the indolent nature of the disease, is a very good option for these patients which offers some practicality, and as long as they are well tolerated, offer the way to keep patients with a normal lifestyle.

Among the different agents, PI3 kinase are good oral agents offering a response rate in about half of the patients, but very few patients had a complete response. Furthermore, they are accompanied by a spectrum of side effects, which are on-target side effects based on these agents, including some neutropenia, higher risk of infections, and some GI symptoms.

Recently, tazemetostat, which has been approved, has been approved based on the phase 2 study that recruited patients with different profiles. This phase 2 study has shown that this agent is active in patients with a mutation in the EZH2 gene and more than two-thirds of the patients receiving this agent that carries this mutation in the tumor had a response to this agent, and this response started to last over one year.

The safety of this compound was pretty interesting with rather grade 1 and 2 side effects such as fatigue, a few hematological parameters going down, but in general, it was very well tolerated. There were only less than 5% of patients undergoing grade 3 or 4 events. So it looks like this is an oral agent that is very well tolerated.

The R^2 regimen is well tolerated despite the side effects usually associated with lenalidomide such as fatigue, neutropenia, and rashes, and obviously, with CAR T cell therapy, we have the usual side effects of these agents.

Dr. Nastoupil:
It sounds like patients have very effective and tolerable and targeted options in the relapse setting. And what I'm hearing is that we're more commonly pursuing these agents after patients might receive frontline chemo-immunotherapy.

So for those of you who are just tuning in, you're listening to CME on ReachMD. I'm Dr. Loretta Nastoupil, and here with me is Dr. Gilles Salle. We're discussing the current and emerging therapeutic landscape for follicular lymphoma.

So thank you for that great overview of the current therapeutic options for relapse/refractory follicular lymphoma. Let's move on to what the future holds. Can you describe some of the emerging therapies including combinations and where they might fit into clinical practice?

Dr. Salles:
Yes. Thank you. This is really an interesting question and given the number of agents we have, we have seen many new agents being brought further in earlier lines of therapy but also different combinations being explored in second line and later.

In first line of therapy, immunochemotherapy followed eventually by maintenance with an anti-CD20 antibody has been the mainstream of patients in need of therapy. But this has been challenged by the combination of lenalidomide and rituximab, the so-called R^2 regimen, which has shown similarity in term of result to the classical immunochemotherapy regimen. Some variations of this regimen exist such as a combination of obinutuzumab plus lenalidomide, for instance.

We have seen in the second-line setting different other options being explored, such as combination of PI3 kinase plus rituximab and different other potential associations.

With the new agents, tazemetostat that we already discussed, there are a couple of interesting combination therapies that are being explored. In second line or subsequent line, there is a combination of tazemetostat plus the R^2 regimen that is currently evaluated in a large, randomized trial, and given the mode of action of tazemetostat, that not only targets a tumor cell itself but also it has an effect on its microenvironment; this could be a very interesting scenario for our patients. Based on some preclinical data, a combination of tazemetostat plus venetoclax will also be of interest and I guess will be examined by a couple of investigators.

Others have sought to bring tazemetostat in the first-line setting, and there is also a clinical trial investigating this combination in the first-line setting. And obviously, this could be also combined with rituximab, and other trials are exploring this avenue.

So I will say that given the safety profile of tazemetostat, which in my mind is one of the best-tolerated oral targeted agents we have right now, we have many opportunities to explore new combinations that obviously need to be further evaluated for their safety and efficacy in the near future and remain investigational at this time.

Dr. Nastoupil:
I think you raised a really interesting point with the number of combinations you just described. It does suggest that we might harness

the multiple modes of action of tazemetostat, including its impact on the microenvironment, and choosing its partner may help differentiate or potentiate those different mechanisms of action and see activity, particularly in those wild-type populations. And as you mentioned, the toxicity profile lends itself very favorably to combination strategies.

I think that's going to make our next question even more complex. As we have more and more combination strategies moving into clinical trials right now, there's considerable uncertainty regarding the optimal sequencing of therapies in the relapse/refractory setting. Can you share strategies to our listeners so that they might have more confidence when faced with these complex and numerous decisions?

Dr. Salles:
This is a complex question given the variety of clinical presentation and clinical course of patients with follicular lymphoma. What we have learned recently is that many patients will have a long survival as long as a first line of therapy had been efficient or even if they were on watch-and-wait if they don't progress early. So there is the majority of patients that actually respond well to first-line therapy and will present with many options in the second-line setting. For these patients, the disease is probably very indolent, and as long as we rule out the possibility of histological transformation, I will favor the opportunity of using these oral non-chemotoxic non-cytotoxic agents.

So one of the options is obviously the R^2 regimen or its variations which has been well documented and well established. Tazemetostat is a good option for patients that carry in the third-line setting an EZH2 mutation. And for those who do not carry this mutation, it's an option when you have potentially eliminated the other options. PI3 kinase will fit also well in this setting.

For those patients that have early relapses after immunochemotherapy or early failure of another approach, it's probably a good time to discuss immunochemotherapy if they haven't received it or to discuss different combination. But what I have found interesting with the different new agents being developed in the field of follicular lymphoma, is that many of them retain an important activity in patients with early progression after immunochemotherapy. This was the case of the R^2 regimen of tazemetostat and of some other PI3 kinase. So it seems that we can change the paradigm even for these patients by developing new agents for them.

Dr. Nastoupil:
So despite having a lengthy list of options, it sounds like patient-specific characteristics, including their response to prior lines of therapy, whether they harbor the EZH2 mutation, and potentially their comorbidities may indeed factor into treatment selection. But again, having several options is always good for patients.

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

Dr. Salles:
Well, my take-home message is that we have ways to move away from the classical cytotoxic agents, and we should for each single patient try to individualize the therapy and discuss with them the different options that are possible. And this will provide them very good care.

Dr. Nastoupil:
And it sounds like, as you've mentioned, there are a number of targeted agents that hold promising efficacy and more favorable toxicity, particularly when we consider the numerous rounds of chemotherapy approaches we've utilized in the past 10 to 15 years. Very optimistic that these are, again, favorable changes for patients. And I'm actually not disappointed that we have the challenges facing us in terms of selecting amongst all of these different options. But again, I'm very encouraged to see that we're learning more about the biology of the disease that may potentially inform that treatment selection.

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

Dr. Salles:
Thank you, Dr. Nastoupil. I'm looking forward to meeting again.

Announcer:
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