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

Navigating CLL Treatment: A Deep Dive into Efficacy and Safety

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

Dr. Russell:
This is *Project Oncology* on ReachMD, and I'm Dr. John Russell. Here with me today to discuss the safety and efficacy of therapies for chronic lymphocytic leukemia, or CLL for short, is Dr. Seema Bhat. In addition to being an Associate Professor in the Department of Internal Medicine in the Division of Hematology at Ohio State University, she also specializes in treating patients with CLL at the Ohio State University Comprehensive Cancer Center-James. Dr. Bhat, thank you for being here today.

Dr. Bhat:
Thank you, Dr. Russell, for that introduction. And thank you for having me.

Dr. Russell:
To begin, Dr. Bhat, can you give us an overview of the different treatment options available for CLL and their optimal sequencing?

Dr. Bhat:
I love to answer this question. That's because treatment for CLL has improved majorly over the last decade. We have moved away from the traditional chemoimmunotherapy to targeted agents in the last decade, and the landscape has completely changed. Compared to chemotherapy, survival as well as duration of time the disease remains under control with these agents has increased.

Broadly, we divide the treatment into two groups. The first one is called BTK, or Bruton's tyrosine kinase, inhibitors, for which we now have four approved agents. We have ibrutinib, acalabrutinib, and zanubrutinib. These are called the covalent BTK inhibitors. And now we have pirtobrutinib, which was recently approved in December of 2023. And this is a noncovalent BTK inhibitor. The other group of targeted agents is the BCL-2 inhibitor, of which we have one approved FDA agent, and that's venetoclax. Then we have monoclonal antibodies which are directed against the CD20 antigen. And there, we have rituximab and obinutuzumab.

As far as sequencing is concerned, we are still learning about that. A patient who needs treatment for CLL will likely require or go through both these classes of drugs through his or her treatment history. Paying attention to the patient characteristics, disease characteristics, and patient preference will help determine the frontline treatment.

Now, a patient who is progressing on a covalent BTK inhibitor will need to switch to another class of drugs. Whereas a patient who is progressing after completing 1 year of venetoclax plus obinutuzumab may be retreated if the progression happened a few years after completion of the initial treatment.

Dr. Russell:
So with those approaches in mind, could we zero in on safety and efficacy profiles? So if we start with efficacy, what can you tell us about the effectiveness of each of the options you mentioned?

Dr. Bhat:
These targeted agents are very effective treatments, as can be seen by the outcomes with these agents. These agents have been directly compared with chemoimmunotherapy in multiple clinical trials. Every time, those clinical trials have shown that the targeted agent was superior to the chemoimmunotherapy. For example, in two large national clinical trials, ibrutinib was compared to chemoimmunotherapy; in patients younger than 65, the chemoimmunotherapy was FCR, and in patients older than 65 years of age, the chemoimmunotherapy was bendamustine plus rituximab. And in both of these studies, ibrutinib was shown to have superior efficacy.

And similarly, acalabrutinib and zanubrutinib have been compared in separate studies with chemoimmunotherapy, which again showed that these targeted agents were superior to the chemoimmunotherapy.

Venetoclax, the BCL-2 inhibitor that is used in combination with obinutuzumab, was compared to chemoimmunotherapy in the CLL14 study. And long-term data from this study continues to show superiority of venetoclax with obinutuzumab. This is in the frontline setting. Even in the relapsed and refractory setting, the targeted agents have repeatedly shown superiority compared to chemoimmunotherapy.

Dr. Russell:
And how about their safety? What are some of the common side effects associated with those treatment options?

Dr. Bhat:
Overall, these agents are very well tolerated. With BTK inhibitors, we may see fatigue come up, we may see body aches, muscle pains, and we may see diarrhea. All of these are usually low grade and very manageable.

Some of the side effects that are very specific for BTK inhibitors are effects on the heart and an increased risk of bleeding. These drugs can cause changes in heart rhythm, especially what is called atrial fibrillation, where the heart beats fast and irregularly. The risk of atrial fibrillation is greatest with ibrutinib. So nowadays, we actually prefer acalabrutinib and zanubrutinib over ibrutinib.

As far as venetoclax is concerned, the major risks with this drug is at the start of treatment when it can cause what is called TLS, or tumor lysis syndrome. Sometimes we need to admit patients, especially those patients who have higher risk of this complication of TLS. We admit them to the hospital and initiate the medication, and we monitor their blood at frequent intervals and take care of these complications, these electrolyte problems, and the uric acid going up as they come. So we have to be aware of this problem and we have to be ready to manage it in an appropriate way.

Other than that, venetoclax is very well tolerated. It can cause changes in blood counts, but usually that's very manageable. It can also cause nausea and diarrhea, which is also very well controlled with supportive medications.

Dr. Russell:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. John Russell, and I'm speaking with Dr. Seema Bhat about the safety and efficacy of therapies for CLL.

Dr. Russell:
So, Dr. Bhat, given the safety and efficacy profiles of each of the treatment options, how do you balance the potential benefits and the possible side effects when you're selecting a therapeutic approach for a patient?

Dr. Bhat:
Given the wealth of different agents that are available to us, we have the luxury to choose a treatment that fits the right patient. For example, if a patient has uncontrolled atrial fibrillation, I will avoid a BTK inhibitor. On the other hand, if a patient has kidney disease, I will not use venetoclax.

Then there are also some disease characteristics that we have to pay attention to; for example, if a patient had high-risk disease like those patients whose CLL has this chromosome 17 abnormality or TP53 mutation, I will prefer to use a BTK inhibitor because research has shown that those patients do better with a BTK inhibitor. On the other hand, if there is a patient who has standard-risk CLL and strongly prefers a fixed duration, 1 year treatment and does not mind coming to the clinic for IV infusions for obinutuzumab, I will give that patient venetoclax plus obinutuzumab. So there are various things that we take into consideration while choosing and discussing treatment options with our patients.

Dr. Russell:
And are there any supportive care strategies we can use to help our patients cope with the side effects they might experience?

Dr. Bhat:
Yes, there are various side effects that our patients may experience, and these medications tend to be long-term medications. So we have to pay attention to the side effects so that their quality of life is not majorly affected. For example, fatigue can be a usual side effect, but we usually start with ruling out other correctable causes of fatigue like thyroid disease, sleep apnea, or even vitamin D deficiency. If anything is found that's correctable, we address that. If the fatigue starts interfering with the daily activities of the patient, then a dose reduction is definitely an option. Likewise, for arthralgias, treating with medications so patients can stay on the treatment is helpful sometimes. Sometimes we can use short courses of steroids, which has been found to be helpful.

Dr. Russell:
So now we're just about out of time for today. But before we close, Dr. Bhat, could you look ahead for just a moment, and what are your

thoughts on the future of CLL therapy? Where do you think we're headed?

Dr. Bhat:
I think we're getting closer to personalized care that is fit for a particular patient. A particular patient may be a good candidate for combination therapy or a doublet therapy, like ibrutinib plus venetoclax, with a duration of treatment determined by their response. Some patients may need it for 2 years, while there are others who may need a combination for a longer period of time. Then there are patients who will be just fine with continuous acalabrutinib or zanubrutinib. So I see the future is moving towards personalized treatment in CLL.

And then we are also recognizing a growing population of treated patients in our clinic whose disease has progressed on both the available targeted agents: the BTK inhibitors and the BCL-2 inhibitors. These are called dual-refractory patients. Research is ongoing to address this. Recently, pirtobrutinib was approved, giving us another good option for treating these patients. And in the coming years, we may see a cellular therapy and more advanced antibodies like bispecific antibodies approved for the treatment of CLL. Our research is ongoing for this, and I'm seeing the field continue to expand, and the options continue to increase for our patients.

Dr. Russell:
Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Seema Bhat, for joining me to discuss the safety and efficacy of therapies for chronic lymphocytic leukemia. Dr. Bhat, it was great having you on the program.

Dr. Bhat:
Thank you for having me.

Announcer:
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