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Considerations for Time-limited Treatment in 1L Treatment Selection Decisions

Announcer:
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Dr. Cortese has received compensation from the US Medical Affairs Department of AbbVie Inc. to prepare and present the following information and is speaking on behalf of himself with input from AbbVie.

Dr. Caudle:
This is ReachMD, and I'm your host Dr. Jennifer Caudle. In today's program, we'll begin by briefly reviewing the updated five-year off-treatment analysis of the CLL14 study of fixed-duration venetoclax plus obinutuzumab, or VenO for short, in first line for chronic lymphocytic leukemia, or CLL for short.

Joining me for this discussion is Dr. Matthew Cortese, who's an Assistant Professor of Oncology with the Departments of Medicine, Lymphoma section with a secondary appointment in Cancer Genetics and Genomics at Roswell Park Comprehensive Cancer Center in Buffalo, New York.

Dr. Cortese, welcome to the program.

Dr. Cortese:
Thanks for having me.

Dr. Caudle:
Well, before we dive further into our program, let's review the approved indication for venetoclax.

Announcer:
Indication
Venetoclax is a BCL-2 inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia, or CLL, or small lymphocytic lymphoma, or SLL.

Dr. Caudle:
Let's start with a brief look at the CLL14 study that evaluated fixed-duration VenO versus chlorambucil plus obinutuzumab, in patients with previously untreated CLL.[1,2] The primary analysis led to the FDA-approval of VenO for the treatment of adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.[1]And in the updated analysis that was presented at the 2023 summer congresses, we saw that half of patients have the opportunity for five-years off-treatment without progression.[3]

Dr. Cortese, can you review the progression-free survival data for the CLL14 trial?

Dr. Cortese:
Yes, in the CLL14 primary analysis, a one-year fixed duration regimen of VenO reduced the risk of progression or death by 67 percent versus chlorambucil plus obinutuzumab.[1,2]

And at the five year off-treatment period, patients who had received the VenO regimen had a median progression-free survival of 76.2 months versus patients on Obinutuzumab chlorambucil with 36.4 months. With VenO, half of the patients were progression-free for over five years after completing treatment.[3,4]

Another result that stood out to me was that five years after completing treatment, about 65 percent of patients in the VenO arm hadn't yet received a subsequent treatment compared to 37 percent for chlorambucil plus obinutuzumab.[3]

Dr. Caudle:
In considering this CLL14 data, what does the potential time off-treatment mean for you and your patients?

Dr. Cortese:
Being able to offer a treatment where some patients may not need further therapy for five years or more is very important for us as clinicians. You know, I see people who are years off-treatment and, as a provider, I guide them through starting VenO during the one-year on-treatment period. So it's gratifying to both me and the patient when follow-up visits show normal labs and blood cell counts, even several years after completing VenO-based therapy. And I find that it's quite satisfying as a CLL doctor.

Dr. Caudle:
Now turning to the safety data, what were the findings in CLL14?

Dr. Cortese:
The CLL14 primary safety analysis showed that the safety profile of VenO was consistent with the known safety profile of VenO with similar rates of grade three or higher adverse events between treatment arms. The most common adverse reactions greater than or equal to twenty percent for VenO were neutropenia, diarrhea, and fatigue.[1]

Dr. Caudle:
It was also observed that the incidence of select grade three to four adverse events decreased over time from the VenO combination period to the venetoclax single-agent treatment period. And, no new safety signals were identified for the VenO regimen at the five-year off-treatment analysis.[3] What are your thoughts on these safety results and what does this mean for the management of your CLL patients, Dr. Cortese?

Dr. Cortese:
Overall, cytopenias are more likely to appear early on with venetoclax, so we need to monitor patients carefully and be ready to manage them with appropriate dose modifications, growth factors, and if applicable, anti-infective agents. However, the likelihood of adverse events occurring later in therapy is likely to be infrequent, especially after completing treatment when there's no further exposure to venetoclax.

Dr. Caudle:
With the CLL14 data that we reviewed in mind, what are your main considerations for choosing your first-line therapy?

Dr. Cortese:
Of course, my primary concerns are efficacy and toxicity, so I'll consider comorbidities and safety when making treatment decisions. And I always keep in mind the potential for ongoing adverse events, and the duration of exposure to treatment, and potential next line of therapy. So for me, the opportunity to offer my patients time off-treatment is a benefit. Then, after evaluating the treatment options, I have a discussion with the patient to determine their preferences, including their goals of care, such as quality of life.[5–7]

Many patients don't want to be on therapy indefinitely, and so the potential for time off-treatment is not only something I'd be considering in treatment selection, but I'd also want to know if it was important to my patient.[8,9]

Dr. Caudle:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle, and today I'm speaking with Dr. Matthew Cortese about time off-treatment opportunities in first-line CLL treatment selection.

Since you mentioned quality of life as being among your patients' goals of treatment, do we know anything about the quality-of-life assessments in the CLL14 study?

Dr. Cortese:

So we can look at the patient reported outcomes data from CLL14, which was evaluated using the European Organization for Research and Treatment Core Quality of Life Questionnaire. This 30-item cancer questionnaire asks responders to rate the severity of symptoms, function, global health status, and quality of life burden over the last seven days at baseline, day one of each treatment cycle, and day 28 of prespecified cycles during follow-up after treatment completion.[10]

Please note these patient-reported outcomes were exploratory and weren't powered to detect statistical differences between the arms, so we can't draw comparative conclusions from the data.[10]

Now improvement in global health status or quality of life was observed as early as cycle three with VenO and by cycle eight with chlorambucil plus obinutuzumab. And this improvement in the VenO arm was maintained through end-of-treatment and off-treatment follow-up.[10]

Turning to symptom scales, improvement in fatigue was seen as early as cycle three in the VenO arm and cycle six in the chlorambucil arm. And this improvement was maintained through the end of treatment and off-treatment follow-up.[10]

In addition, improvement in insomnia was also reported as early as cycle three with venetoclax and cycle four with chlorambucil. Similar to fatigue, the improvement in insomnia was maintained through the end of VenO treatment and during off-treatment follow-up.[10]

Dr. Caudle:
How do these patient reported outcomes impact your first-line treatment selection decisions?

Dr. Cortese:
To me, this data are crucial for how I consider treatment selection. It's important to care how patients feel throughout their treatment journey since CLL is a mostly a chronic condition,[11] so I want my patients to not only live a long life but also have a good quality of life.

Efficacy and safety are my primary considerations in first-line treatment selection, but there are multiple effective first-line treatment options available and no clear evidence of one being superior. At that point, additional factors such as quality of life and reduced treatment exposure become particularly valuable to consider for me and my patients.

Announcer:
The Patient Reported Outcome endpoints are exploratory and not powered to control for type-I error. The defined thresholds for quote-unquote "improvement", "stable", and "worsening" may not correlate with clinically meaningful differences. The Patient Reported Outcome results may be confounded by events not related to disease or treatment.

Dr. Caudle:
You mentioned that additional factors after safety and efficacy are important to consider, so are you thinking about the next therapy choice after first-line, even at the beginning of the patient's treatment journey?

Dr. Cortese:
When choosing first-line treatment, we have to consider future options. I plan to see my patients in the community for years, so I definitely think about long-term decisions. So my strategy in selecting and sequencing treatment is to optimize clinical outcomes throughout a patient's treatment journey. In my practice, I factor in comorbidities, such as cardiovascular risk and renal function, which are crucial for older patients.

In addition, I also consider patient preferences and the ability to treat in a time-limited fashion when selecting a treatment.

Dr. Caudle:
Now we're just about out of time, so do you have any key takeaways you'd like to leave with our audience today, Dr. Cortese?

Dr. Cortese:
I appreciate the cumulative data in the six-year CLL study update, that even five years after completing treatment, just over half of the patients are still progression-free. To me, this demonstrates the potency and durability of progression-free survival with VenO, even with time off-treatment.[3]

Dr. Caudle:
Well your insights have given us a lot to consider as we come to the end of today's discussion. But before we close, please stay tuned to hear some important safety information.

Announcer:
Important Safety Information

Contraindications

- **Strong CYP3A Inhibitors:** Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with CLL/SLL is contraindicated.

Warnings and Precautions

- **TLS:** Tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in patients treated with venetoclax. Anticipate TLS; assess risk in all patients. Premedicate with anti-hyperuricemics and ensure adequate hydration. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases.
- **Neutropenia:** Monitor blood counts. Interrupt dosing and resume at same or reduced dose. Consider supportive care measures.
- **Infections:** Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with venetoclax. Monitor patients for signs and symptoms of infection and treat promptly. Withhold venetoclax for Grade 3 and 4 infection until resolution and resume at same or reduced dose.

Warnings and Precautions continued

- **Immunization:** Do not administer live attenuated vaccines prior to, during, or after venetoclax treatment until B-cell recovery.
- **Embryo-Fetal Toxicity:** May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.
- **Increased mortality in patients with multiple myeloma (MM) when venetoclax is added to bortezomib and dexamethasone.** In a randomized trial in patients with relapsed or refractory MM, the addition of venetoclax to bortezomib plus dexamethasone, a use for which venetoclax is not indicated, resulted in increased mortality. Treatment of patients with MM with venetoclax in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Adverse Reactions

- In CLL/SLL, the most common adverse reactions (≥20%) for venetoclax when given in combination with obinutuzumab or rituximab or as monotherapy were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema.

Dr. Caudle:
And with that important safety information, I'd like to thank my guest, Dr. Matthew Cortese, for helping us better understand the potential benefits of time-limited treatment when considering therapy for patients with CLL in first-line and beyond.

Dr. Cortese, it was great speaking with you today.

Dr. Cortese: Thanks for having me.

Announcer:
This medical industry feature was sponsored by AbbVie Oncology US Medical Affairs. If you missed any part of this discussion or to find others in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge.

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