Transcript Details
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Key Considerations for Initiating a Chronic Lymphocytic Leukemia Therapy

Announcer:
Welcome to ReachMD. The following program, “Key Considerations for Initiating a Chronic Lymphocytic Leukemia Therapy” is developed and sponsored by AbbVie. This activity is intended for United States and Puerto Rico health care professionals only.

The following speaker 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 AbbVie.

Dr. Nodzon:
I am Dr. Lisa Nodzon, an advanced oncology certified nurse practitioner in the Department of Malignant Hematology at Moffitt Cancer Center in Tampa, Florida.

I want to spend a few minutes with you today on reviewing the venetoclax dose ramp-up in CLL.

No matter whether you are using venetoclax in the first-line setting with obinutuzumab or in the relapsed/refractory setting with rituximab or as monotherapy, patients will require a 5 week dose ramp-up, starting with 20 mg once daily for the first week, and increasing weekly to 50 mg, 100 mg, 200 mg, and finally reaching the recommended daily dose of 400 mg.

So, let’s start off by discussing why venetoclax has a 5-week dose ramp-up in CLL in the first place. The 5-week dose ramp-up was designed to reduce the risk of tumor lysis syndrome, or TLS.

TLS is a consequence of tumor cell breakdown in response to therapy in which the electrolytes from the intracellular contents of the cell are released into the peripheral blood. If the kidneys are unable to keep up with such a demand, this may result in hyperkalemia, hyperuricemia, hypocalcemia, or hyperphosphatemia, which could lead to serious clinical complications, such as cardiac arrythmias and acute renal failure.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Impaired renal function further increases the risk. In order to help prevent TLS during the 5-week dose ramp-up there are prophylaxis and monitoring measures to perform as your patients begin treatment.

Announcer: Splenomegaly may also increase the risk of TLS. After dosage interruption, reassess for TLS risk and follow the dose modification guidance in the prescribing information when restarting patients on venetoclax.

Dr. Nodzon:
Let’s discuss these measures in more detail. First, all patients need a baseline assessment to help determine the risk of TLS, including absolute lymphocyte count and CT scan to determine the size of all the lymph nodes, as well as blood chemistries including potassium, uric acid, phosphorus, calcium, and serum creatinine. You’ll want to correct any pre-existing blood chemistry abnormalities before initiating venetoclax. It's also important that patients are adequately hydrated before and throughout therapy along with initiation of an appropriate antihyperuricemic agent, such as allopurinol, at least 48h prior to initiating venetoclax. The recommended hydration volume is 6 to 8 glasses of water each day, which is roughly 56 ounces total, however should be individualized based upon patient’s comorbid conditions. Patients should be assessed along with maintaining of adequate hydration before and throughout venetoclax therapy.

Next, let's talk about labs. Because changes in blood chemistries consistent with TLS can occur as early as 6 to 8 hours after the first dose of venetoclax and with each dose increase, you'll need to perform lab assessments pre and post dosing during the dose ramp-up per labeling instructions. Again, we're looking at potassium, calcium, serum creatinine, phosphorus, and uric acid. First you'll need to determine if the patient's tumor burden is LOW, MEDIUM, or HIGH. A patient is considered LOW if their baseline absolute lymphocyte count is under 25 thousand per microliter and all lymph nodes are smaller than 5 cm. If the patient has any lymph nodes 5 cm to less than 10 cm OR an absolute lymphocyte count that is greater than or equal to 25 thousand per microliter, they would be considered MEDIUM tumor burden. A HIGH tumor burden patient would have any lymph node greater or equal to 5 cm and an absolute lymphocyte count greater than or equal to 25 thousand per microliter, OR have a lymph node 10 cm or larger.

LOW and MEDIUM tumor burden patients can begin venetoclax in an outpatient setting. For the first dose of the 20 mg and 50 mg tablets, assess labs pre-dose and at 6 to 8 and 24 hours post-dose. When ramping up to subsequent doses, check pre-dose labs or more often as clinically warranted. Always review results in real time and promptly manage any abnormalities. For MEDIUM tumor burden patients, you may also want to also consider additional IV hydration; and if their creatinine clearance is less than 80 mills per minute, you may want to consider monitoring in the hospital setting. We've found that the majority of patients we see have LOW or MEDIUM tumor burden and can start venetoclax in the outpatient setting.

For patients with HIGH tumor burden the monitoring should be done in the hospital at pre-dose, and at 4, 8, 12, and 24 hours post-dose for the first dose of 20 mg and 50 mg. Give HIGH tumor burden patients both IV and oral hydration, and for subsequent ramp-up doses, check labs pre-dose, and at 6 to 8 and 24 hours post-dose. You may also want to consider rasburicase if baseline uric acid is elevated.

It's important to think about the timing of the labs. For example, if a LOW or MEDIUM tumor burden patient is going to start venetoclax on Monday, hydration and antihyperuricemics are initiated on the previous Friday and continued throughout the entire ramp-up period. On Monday morning, a pre-dose lab draw may be conducted at 8am, which means the patient will come back between 2pm-4pm for the next round of labs and so forth.

Another important consideration prior to starting patients is to understand the patient's medication list in order to check for potential drug interactions, in particular the strong CYP3A inhibitors which are contraindicated during the CLL dose ramp-up due to the potential for increased risk of TLS. I've found that it's really helpful to work closely with the pharmacist on this. Some common examples of strong CYP3A inhibitors include anti-fungal drugs such as posaconazole and voriconazole, as well as some antibiotics such as clarithromycin.

On the other hand, P-gp inhibitors or moderate CYP3A inhibitors can still be used with caution during the 5-week dose ramp-up, but the recommendation is to reduce the dose of venetoclax by at least 50 percent throughout the time the patient is on the interacting medication. You can resume the venetoclax dose that was used prior to initiating the CYP3A or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor. Again, the pharmacist is a valuable resource to help ensure you're dose adjusting appropriately. You'll want to check the prescribing information for additional information on drug interactions and dose adjustments. Patients should be advised to maintain an up to date medication list with all of their dispensing pharmacies.

Well, I hope you've found this overview of the CLL dose ramp-up with venetoclax useful and have gained a better understanding of the ramp-up, hydration and TLS prophylaxis and monitoring measures required when initiating your CLL patients on venetoclax.

Please stay tuned for important safety information. Thank you.

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).

Contraindications

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

Warnings and Precautions

- **TLS:** Tumor lysis syndrome (or 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, and 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.
- **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 (or 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 and 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.

Review full prescribing information for additional information at www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110 or go to abbviemedinfo.com.

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