Transcript Details
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The Ramp-Up & Dosing of an Acute Myeloid Leukemia Therapy

Announcer:

Welcome to ReachMD. The following program, "The Ramp-up & Dosing of an Acute Myeloid 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.

Ilene Galinsky:

Hi, I'm Ilene Galinsky, Senior Program Research Nurse Practitioner for the Leukemia Program at the Dana Farber Cancer Institute and I'll be talking about the ramp-up and dosing for venetoclax therapy in patients with newly diagnosed AML.

In AML, venetoclax dose depends on the combination partner. When combined with hypomethylating agents such as azacitidine or decitabine, the venetoclax ramp-up is a 3-day daily ramp-up to a final 400 mg daily dose. When combined with low-dose cytarabine, there is a 4-day venetoclax daily ramp-up to a final 600 mg daily dose.

In either case the combination partner is initiated on day 1 of venetoclax dosing, and the combination therapy is continued until disease progression or unacceptable toxicity is observed.

An important point here is that, due to the acute nature of AML, this ramp up dosing period for AML over 3 or 4 days differs from the ramp up for CLL, which is over several weeks.

But since venetoclax can cause a rapid reduction of tumor burden there's a potential risk for tumor lysis syndrome, or TLS, in patients with AML.

For this reason, patients shouldn't be initiated on venetoclax therapy until their white blood cell counts are less than 25,000, which means that cytoreduction may be required prior to treatment to bring white blood cell counts below 25,000.

Hospitalization protocols for the initiation of venetoclax therapy will vary depending on your institution's practice standards and status of each patient, but in my practice I recommend that all patients be put on allopurinol before starting therapy and evaluate the need for rasburicase.

I also maintain good fluid intake either intravenously or PO at 2 liters per day. These prophylactic measures should be continued during the ramp-up phase. I monitor blood chemistries every 6 to 8 hours during the ramp-up and 24 hours after reaching the final dose, including potassium, uric acid, phosphorus, calcium, and creatinine.

Additional measures should be taken for patients with risk factors for TLS, such as circulating blasts, high burden of leukemia involvement in the bone marrow, elevated pretreatment LDH levels, or reduced renal function. For these patients, we'll often monitor fibrinogen and CRP levels. We may also consider reducing the venetoclax starting dose.

We then continue to monitor for evidence of TLS during treatment, and we manage abnormalities in serum creatinine, uric acid and electrolytes quickly if they develop.

Lastly, I want to spend a minute on drug-drug interactions with venetoclax.

Since venetoclax is predominantly metabolized by CYP3A, concomitant use with strong or moderate CYP3A or P-gp inhibitors increases venetoclax exposure, which can increase the risk of TLS at initiation and during the ramp-up phase. And this requires venetoclax dose adjustments during and after ramp-up.

Let's consider the use of the antifungal prophylaxis agent Posaconazole, which is a strong CYP3A inhibitor. Based on the outcomes of the posaconazole sub study within the M14-358 trial, it was determined that the optimal dosing of venetoclax in combination with posaconazole should not exceed 70 mg. For other strong CYP3A inhibitors, it's recommended to reduce the venetoclax dose to 100 mg.

Moderate CYP3A and P-gp inhibitors, when taken concomitantly with venetoclax, require a reduction in the venetoclax dose by at least 50%.

One must also keep in mind that grapefruit products, Seville oranges, and starfruit contain inhibitors of CYP3A as well, so these should be avoided during the treatment of venetoclax.

An important point: antifungal prophylaxis can also be continued during venetoclax treatment with the use of agents not classified as CYP3A or P-gp inhibitors, such as the echinocandins like Micafungin, Caspofungin, and Anidulafungin.

But in all cases, we want to verify the drug profiles of our patients and monitor closely for signs of venetoclax toxicities, resuming the venetoclax dose that was used prior to initiating any CYP3A or P-gp inhibitor 2 to 3 days after discontinuation of that inhibitor.

In summary, when we initiate venetoclax in patients with newly diagnosed AML, the dose is ramped-up to a final 400 mg daily dose over the course of 3 days when combined with AZA or DEC. Before starting venetoclax and during the ramp-up period, it's important to provide TLS prophylaxis with hydration and anti-hyperuricemics, assess and correct blood chemistries, and consider appropriate dose modifications.

Now let's take a moment to review the indication and safety summary for venetoclax.

Announcer:
Venetoclax Indication and Safety Overview for AML
Indication

Venetoclax is a BCL-2 inhibitor indicated:

- In combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults:
  - who are age 75 years or older, or
  - who have comorbidities that preclude use of intensive induction chemotherapy.

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 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 (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 **AML**, the most common adverse reactions (≥30%) in combination with azacitidine, or decitabine, or low-dose cytarabine were

nausea, diarrhea, thrombocytopenia, constipation, neutropenia, febrile neutropenia, fatigue, vomiting, edema, pyrexia, pneumonia, dyspnea, hemorrhage, anemia, rash, abdominal pain, sepsis, musculoskeletal pain, dizziness, cough, oropharyngeal pain, and hypotension.

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.

Announcer:
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