Transcript Details
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Advances in AML: The Role of a BCL-2 Inhibitor in Current Treatment Paradigms

ReachMD Announcer:
Welcome to ReachMD. The following program, “Advances in AML: The Role of a Targeted Therapy in Current Treatment Paradigms” is developed and sponsored by AbbVie. This activity is intended for United States and Puerto Rico health care professionals only.

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Dr. Turck:
For over 40 years, the treatment of acute myeloid leukemia, or AML, was relatively straightforward. Clinicians needed to decide whether the patient was fit or unfit for therapy and proceed with standard high-intensive chemotherapies or low-intensity regimens instead.

But with the development of technologies paired with an enhanced understandings of the AML genomic landscape, it’s become possible to identify clinically relevant molecular aberrations and develop targeted AML therapies. On today’s program, we’ll explore one such therapy and its role in current AML treatment paradigms.

This is ReachMD, and I’m Dr. Charles Turck. Joining me is Dr. Uma Borate, hematologist at Ohio State University, Wexner Medical Center, and Dr. Harry Erba, director of the Leukemia Program at the Duke Cancer Institute in Durham, North Carolina.

Doctors, welcome to the program.

Dr. Borate:
Thank you.

Dr. Erba:
Thank you. I’m happy to be here and join my colleague, Dr. Uma Borate.

Dr. Turck:
Starting with you, Dr. Erba, would you briefly explain how our deeper understanding of AML’s pathogenesis has affected treatment approaches?

Dr. Erba:
Of course. Our increased understanding of the pathogenesis of AML has spurred the development of compounds in the treatment of AML, particularly the creation of small molecules that target the disease on a molecular level.

The mutational profile of AML suggests that epigenetic modulation of gene expression is critical to disease development. This is because the broadest class of mutations includes chromatin modifiers, spliceosome mutations, and transcription factors. We still have much to understand about how these epigenetic modulations contribute to disease through the various mutations, which are often loss-of-function mutations.

Current drugs have been designed to inhibit gain-of-function mutations. Targets of interest include such as FLT3, IDH1/IDH2. Other targets of interest include CD33, Hedgehog pathway signaling, and Bcl-2.

Among patients with newly diagnosed AML, those who are eligible for intensive chemotherapy may receive midostaurin, which targets FLT3, or gemtuzumab, which targets CD33, in combination with cytarabine and anthracycline. Among those who are ineligible for intensive chemotherapy, treatment options include gemtuzumab; ivosidenib, which targets IDH1; glasdegib, which targets the Hedgehog pathway, plus low-dose cytarabine; or venetoclax, which targets Bcl-2, in combination with azacitidine, decitabine, or low-dose cytarabine.

Dr. Turck:
And now that we have that background, Dr. Borate, let's focus on the treatment option, venetoclax, among the targeted therapies which Dr. Erba just spoke to. Would you give us an overview of venetoclax?

Dr. Borate:
Certainly. Venetoclax is a Bcl-2 inhibitor indicated in the combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of newly diagnosed AML in adults aged 75 years or older, or those who have comorbidities that preclude the use of intensive induction chemotherapy.

The Viale-A clinical trial was designed to evaluate the efficacy and the safety of venetoclax in combination with azacitidine in 286 patients compared with azacitidine plus placebo in 145 patients. Ven+AZA showed a statistically significant overall survival advantage with a median overall survival of 14.7 months compared with 9.6 months for AZA+PBO. CR + CRh rates were 65% versus 23% for the Ven+AZA and PBO+AZA arm, respectively.

In the Ven+ AZA arm, the median duration of CR or CRh was 17.8 months. Of patients with baseline transfusion dependence, 49% became independent.

The Viale-C trial was designed to evaluate the efficacy and the safety of venetoclax in combination with LDAC vs placebo with LDAC in patients 75 years or older or with comorbidities that preclude the use of intensive induction chemotherapy with the primary endpoint of overall survival. In this study, Ven+LDAC did not significantly improve OS as compared to PBO+LDAC.

Efficacy of the regimen was established based on the rate of CR and duration of CR with supportive evidence of rate of CR+CRh, duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence.

The CR+CRh rates were 47% versus 15% for the Ven+LDAC arm and the pbo+LDAC arm, respectively. The median duration of CR or CRh was 11.1 months versus 6.2 months in the Ven+LDAC arm and pbo+LDAC arms, respectively.

In both studies, the most frequent adverse events were hematologic and gastrointestinal in nature.

Dr. Turck:
And turning back to you now, Dr. Erba, what do we need to know about starting AML patients on this therapy?

Dr. Erba:
In AML venetoclax dose depends on the combination partner. When combined with 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, the venetoclax ramp-up is a 4-day venetoclax daily ramp-up to a final 600 mg daily dose. The combination partner is initiated on day 1 of venetoclax dosing and venetoclax + HMA or LDAC is continued until disease progression or unacceptable toxicity is observed.

All patients should be assessed for their level of risk for TLS and be provided hydration and antihyperuricemics prior to receiving their first dose of venetoclax to reduce the risk of TLS.

It's important to keep in mind potential drug interactions with strong and moderate CYP3A inhibitors. These include the macrolide antibiotics, the antivirals, and the azole antifungals.

Dr. Turck:
Dr. Erba, do you use azole anti-fungals in these patients?

Dr. Erba:
We do. We have a high incidence of fungal infections where we are located. There are clear dosing modifications for the azole antifungals. It's important to partner with your pharmacist to ensure that these drug-drug interactions are recognized and that there are clear dosing recommendations based on these concomitant medications that your patients may be taking.

Dr. Turck:
And once our patients have started this therapy, Dr. Borate, what complications or adverse reactions should we be on the lookout for?

Dr. Borate:

Absolutely. Venetoclax can cause a rapid destruction of tumor cells, which poses a potential risk for tumor lysis syndrome, also known as TLS, in patients with AML. All patients should have a white blood cell count less than 25,000 prior to initiation of venetoclax. Cytoreduction prior to treatment may be required. For patients with risk factors of TLS, additional measures should be considered, including increased laboratory monitoring and reducing the starting dose of venetoclax.

In patients treated with venetoclax plus azacitidine,1.1% experienced TLS events. And in patients treated with LDAC the incidence of TLS was 5.6% and included deaths and renal failure.

Recommended dose modifications based on toxicity vary based on whether the adverse event occurs before or after the patient achieves remission.

If hematological toxicities, such as neutropenia or thrombocytopenia, occur prior to remission, in most cases, treatment should not be interrupted. If hematological toxicity occurs after remission, treatment should be delayed. In case of subsequent occurrences, the cycle may also be reduced by 7 days. For example, instead of a 28 days of venetoclax treatment, patients will receive 21 days of venetoclax treatment in each 28-day cycle.

Neutropenia can be managed with dose interruption and/or the administration of growth factors, if that is part of your institution's practice.

If grade 3 or 4 non-hematological toxicities occur, venetoclax should be interrupted if not resolved with supportive care. Upon resolution to grade 1 or baseline levels, venetoclax may be resumed at the same dose.

Dr. Erba, do you ever consider outpatient therapy, and if so how do you decide whether a patient may be able to receive this therapy in the outpatient setting?

Dr. Erba:
I consider outpatient therapy if the white count is low, if the patient lives close by, they have a caregiver, and if the patient is compliant. Of course, I do this with careful monitoring of electrolytes before they leave the clinic after their first day. Many clinicians do this for patients with CLL.

Dr. Turck:
And just to bring all of this together, I'd like to get your respective takeaways on treatment options for patients with AML based on our discussion today. Dr. Erba, let's start with you.

Dr. Erba:
Thank you. We now have available a therapeutic regimen for older, less fit patients with AML that contributes to a high response rate and a quicker time to achieving remissions than with low-dose Ara-C or HMA alone in the past. Therefore, I think more older patients with AML should be considered for therapy.

Although the response rates are higher than what we have typically seen with HMAs, there are still some very important safety issues of which the practicing physician needs to be aware. Tumor lysis syndrome should be anticipated and prophylactically treated. Myelosuppression is clearly seen with this regimen, and there are a number of options for managing this. Drug-drug interactions are also important to consider.

If you are considering starting a new regimen for your patient, consider consulting with other physicians who have experience with this regimen.

Dr. Turck:
And how about you, Dr. Borate? What message would you like to leave with our audience?

Dr. Borate:
We now have multiple of options available, utilizing various combinations of venetoclax with lower intensity chemotherapy that show improved response rates, for the treatment of AML patients who are unfit for intensive chemotherapy

Dr. Turck:
Well that's a great way to round out our discussion exploring targeted therapies for our patients with AML, and I want to thank my guests, Dr. Uma Borate and Dr. Harry Erba for helping us better understand venetoclax as a treatment option for these patients.

Please stay tuned for important safety information.

ReachMD 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.

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AbbVie | BCL2-US-00044-MC | Version 1.0 | February 2021