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Positive Quality Intervention: Optimizing Venetoclax Treatment of Acute Myeloid Leukemia

Description: The purpose of this PQI is to highlight processes that can be implemented to minimize delays when treating acute myeloid leukemia (AML) with combination venetoclax and hypomethylating agent (HMA) therapy. Additionally, it will review the optimization of venetoclax treatment initiation and ongoing patient management.

Background: Acute myeloid leukemia (AML) is a hematologic malignancy resulting from inappropriate expansion of leukemic myeloid precursor cells in the bone marrow, peripheral blood, and/or other tissues. It accounts for the largest number of adult leukemia deaths in the United States and remains the most common cause of adult leukemias. With an average age at diagnosis of 69 years, many newly diagnosed AML patients require less intensive induction therapy. Novel therapies, such as the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax in combination with an HMA, represent effective, guideline-recommended treatment for these patients. [1-4] Specifically, venetoclax plus azacitidine demonstrated improved overall survival in newly diagnosed AML patients ineligible for intensive induction therapy. This regimen is considered standard of care in this patient population and is endorsed by the National Comprehensive Cancer Network (NCCN®) guidelines.[3,7] Due to the acute nature of this malignancy, there is a need to initiate therapy rapidly. However, starting patients on oral oncolytics such as venetoclax may be associated with barriers such as distribution access necessitating sending prescriptions to an outside pharmacy, insurance approval, and patient cost.[5] Additionally, while many AML patients can initiate venetoclax therapy as an outpatient, some patient-specific factors, including risk of tumor lysis syndrome (TLS), severity of baseline disease, and need for frequent transfusion, may necessitate an inpatient admission for observation.

Creating a reliable framework to minimize delays in venetoclax treatment initiation, as well as supporting continued therapy, can aid in expediting patient care and maximizing clinical outcomes while on treatment. Delays in obtaining venetoclax may negatively impact outcomes as pre-clinical models suggest the apoptotic synergy mechanism is derived from initiating venetoclax concomitantly with azacitidine.[7]

Once a patient with AML is started on venetoclax + HMA therapy, ongoing patient management and proper monitoring are critical to optimize outcomes and mitigate treatment-related adverse effects. Necessary considerations include coordination of appropriate response assessment, including performing a bone marrow biopsy in the first cycle of therapy, ongoing monitoring for myelosuppression and GCSF support to ensure adequate dose pauses, and preventing infection with antibiotic/antifungal prophylaxis bearing in mind possible CYP3A4 mediated drug-drug interactions.[8]

PQI Process:

- Initial patient assessment and treatment considerations
    - Upon AML diagnosis and decision to initiate venetoclax therapy, all new venetoclax prescriptions will trigger a pharmacy consult
    - The pharmacist will collaborate with the provider to:
        - Manage the risks of TLS and infection by recommending appropriate prophylaxis (e.g., antihyperuricemics, antiemetics, antimicrobials, and other supportive care)
        - Determine whether the patient should start treatment as an inpatient or outpatient accounting for TLS risk and necessary monitoring, transfusion threshold, ease of hospital access, etc.
        - Establish a dosing schedule and recommend dose adjustments to account for potential drug interactions
        - Review the monitoring requirements, including the timing of bone marrow biopsy (BMB) and various laboratory tests such as complete blood cell count (CBC), blood chemistry, etc.
- Medication dispensing and coordination of care
    - Pharmacist or pharmacy technician will obtain the patient's insurance information, identify the patient's specialty pharmacy, and initiate a search for any potential patient assistance programs if needed
    - The pharmacist will assist the provider in sending the prescription to the patient's specialty pharmacy, then reach out to the pharmacy to request expedited processing of the prescription
    - Pharmacist and pharmacy technician will work together to:
        - Follow up with any materials necessary for prior authorization (PA; i.e. clinical notes, test results)
            - If patient to be hospitalized for treatment initiation, coordinate with submission of necessary PA documentation if required for inpatient admission
        - Follow up with the patient to acquire information for patient assistance programs if needed
    - Provider will reach out to the insurance company for an urgent peer-to-peer should the medication be denied
    - Once the medication is acquired
        - If patient will be admitted inpatient for venetoclax ramp up dosing, pharmacist and/or nurse navigator to advise patient if they will need to bring their home medication to the hospital to be utilized for treatment
        - Pharmacist and/or nurse navigator to coordinate concomitant initiation of venetoclax and accompanying HMA
- Remission assessment and on-going patient management
    - A bone marrow biopsy to evaluate for remission of disease is recommended between days 21 and 28 of cycle 1 (remission defined as less than 5% leukemia blasts with cytopenia[6]). For patients with resistant disease after cycle 1, repeat BMB evaluations in cycle 2 and beyond should be performed as clinically indicated.
    - In clinical trial, once BMB confirmed a remission, venetoclax was interrupted for up to 14 days or until ANC $\geq$500/µL and platelet count $\geq$50 x 10^3/µL to allow for count recovery [7]
        - See Table 1 for recommended venetoclax dosage modifications for hematologic adverse reactions
        - In clinical practice, adjustment in duration of venetoclax administration per cycle may be instituted once remission is achieved and prior to occurrence of hematologic adverse events
    - Cytopenias are common and recommended management is dependent on remission status (see

Table 1 for management of hematological adverse reactions based on remission status)
    - In clinical trial, supportive care measures including growth factor support were administered as needed per institutional standards[9]
- Designated clinical team member will reach out to patient to either encourage continued adherence to venetoclax dosing schedule or to inform patient if BMB results and/or blood cell counts necessitate treatment hold and/or initiation of supportive care measures

Table 1. Venetoclax dosage modification for hematologic adverse reactions[6]

Adverse Reaction	Occurrence	Dosage Modification
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia	Occurrence prior to achieving remission	In most cases, do not interrupt venetoclax due to cytopenias prior to achieving remission
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent cycle of venetoclax and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax at the same dose in combination with HMA
	Subsequent occurrences in cycles after achieving remission and lasting 7 days or longer	Delay subsequent cycle of venetoclax and monitor blood counts. Upon resolution to Grade 1 or 2, resume venetoclax at the same dose in combination with HMA, and reduce venetoclax duration by 7 days during each of the subsequent cycles, such as 21 days instead of 28 days.

See also Dose Modification Charts for Venetoclax Treatment

Patient-Centered Activities:

- Ensure the patient is informed about the prescription status and availability for pick-up, involving the patient or a family member if needed for communication with the specialty pharmacy
- Provide the Oral Chemotherapy Education (OCE) Sheet
- Review common adverse events especially neutropenia and who to contact with any signs or symptoms of an infection, including fever, chills, sore throat, burning with urination, unusual tiredness, etc.
- Discuss the need for a follow-up BMB between days 21-28 of cycle 1 and provide the patient with contact information for scheduling if needed and advise that medication dose and administration schedule may be subject to change depending on results of biopsy as well as other monitoring labs, i.e. CBC
- If patient to be hospitalized for treatment initiation, review steps in preparation for hospital admission with patient and caregiver
- Regularly follow up with the patient to assess adherence to the treatment regimen, confirm correct venetoclax dosage and schedule, and address how to manage missed doses
    - If venetoclax administration schedule has been adjusted from 28 to 21 days per cycle, reinforce this with patient to make sure they understand which days they are supposed to take the medication

- Consider utilizing a daily dose tracker or calendar for assistance
- Reinforce importance of concomitant administration of venetoclax and HMA and coordinate with infusion staff to ensure patient is aware of HMA administration appointments/schedule
- For more detailed information regarding assessing risk of TLS, ramp up dosing schedule, dose adjustments for drug interactions, patient counseling etc., refer to Venetoclax (Venclexta®) for the Treatment of Acute Myeloid Leukemia PQI
    - Also refer to TLS Risk Assessment Tool
- Neutropenia, including febrile neutropenia, is common due to both the nature of AML disease and treatment
    - Consider use of granulocyte colony stimulating factor (G-CSF) on a per patient basis[10]

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