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Positive Quality Intervention: Venetoclax (Venclexta®) Risk Stratification, Dosing, and Dispensing Procedure

Description: Venetoclax therapy requires particular parameters be closely followed to ensure optimal patient outcomes. This PQI will review appropriate risk stratification, dosing, and dispensing procedures. These risk stratifications create special challenges for the dispensing of venetoclax. Some medium-risk and all high-risk patients may require hospital admission during titration; communication between the oncology pharmacist, nurse, lab technicians, hematologist, and the patient will ensure the recommended administration guidelines and lab monitoring are followed to ensure patient safety and best outcomes.

Background: Venetoclax is indicated in Acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL) and small lymphocytic leukemia (SLL) in patients with or without chromosome 17p deletion. During the ramp-up phase, patients are titrated on venetoclax and assigned a risk category based on tumor burden and potential for developing Tumor Lysis Syndrome (TLS). TLS can occur when there is large tumor burden (large size of any lymph node, or, elevated Absolute Lymphocyte Count (ALC). In patients with CLL treated with single-agent venetoclax, the rate of TLS was 2%. The rate remained consistent for venetoclax in combination with obinutuzumab or rituximab. In patients with AML, the incidence of TLS was 5.6% in combination treatment with cytarabine. Patients at high risk for TLS should be admitted for initiation of venetoclax. Labs that should be monitored according to the manufacturers' guidelines include serum creatinine, uric acid, potassium, phosphorus and calcium. TLS is considered an oncologic emergency.

PQI Process: Upon receipt of a new prescription for venetoclax:

- Determine if the prescriber has assigned a TLS risk category for the patient (see supplemental information)
- If patient falls into the high TLS risk category (or medium risk with CrCl<80 mL/min), coordinate with the prescriber and patient the date and time of admission to the hospital
    - Ensure patient will have medication on hand prior to admission
- CLL/SLL Patients
    - Coordinate with inpatient team timing of necessary lab work (see supplemental information)
    - Labs will need to be ordered for the first dose of 20 mg and 50 mg doses
        - This will occur on two separate admissions
    - Labs need to be drawn pre-dose, 4, 8, 12 and 24 hours after the dose
        - The recommended labs to monitor for TLS are uric acid, serum potassium, serum phosphorus, corrected calcium and serum creatinine
        - Ensure inpatient staff is aware of the lab orders and the frequency so the labs are not seen as "duplicates" and inadvertently cancelled
        - Labs need to be reviewed in "real time" for early detection of TLS
- AML Patients
    - For patients with risk factors for TLS additional measures should be considered, including increased laboratory monitoring and reducing starting dose
    - Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new dose during ramp-up and 24 hours after reaching final dose
    - All AML patients should have a WBC < 25 x 10^9/L prior to initiation of venetoclax
        - Cytoreduction prior to treatment may be required
        - Hospital admission for TLS monitoring should be assessed case by case
    - In select patients, rasburicase may be used for TLS management

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- See **Use of Rasburicase (Elitek®) for Treatment of Tumor Lysis Syndrome** PQI

- **Dosing Guideline:** For all indications assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose and throughout the ramp-up phase to reduce risk of TLS

Venetoclax Ramp-Up Schedule

CLL/SLL§		AML	
Week 1	20 mg	Day 1	100 mg
Week 2	50 mg	Day 2	200 mg
Week 3	100 mg	Day 3	400 mg
Week 4	200 mg	Day 4 and beyond	400 mg or 600 mg*
Week 5 and beyond	400 mg		

§ The CLL/SLL Starting Pack provides the first 4 weeks of venetoclax according to the ramp-up schedule. The 400 mg dose is achieved using 4 x 100 mg tablets supplied in bottles

*400 mg when used in combination with azacitidine or decitabine; 600 mg when used in combination with low dose cytarabine

Patient Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) sheet
- Review titration schedule with patient and provide calendar with dosing schedule and lab appointments
- Confirm if patient has allopurinol prescribed
  - Review that allopurinol should be initiated 2-3 days prior to venetoclax
- Review oral hydration schedule with patient
  - Patient should consume 6 – 8 (8 oz) glasses of water or as instructed by their provider daily starting 2 days before the first dose and throughout the ramp up phase *This is important during the first day of each dose increase*
  - Patients admitted to the hospital will receive IV fluids
  - Outpatients may be considered for IV hydration if oral hydration is inadequate
- For a missed dose:
  - If within 8 hours of the usual time, take as soon as possible and resume normal schedule
  - If greater than 8 hours past the usual time, skip and resume normal schedule the next day
- Confirm with the patient the date, time, and location of hospital if admission is necessary
- Follow up with patient after each dose escalation to confirm patient is taking medications properly
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. VENCLEXTA® (Venetoclax) [Prescribing Information].
2. Larson, R MD and Pui, Ching-Hon MD (2018). Tumor lysis syndrome: Prevention and treatment. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. https://www.uptodate.com/contents/tumor-lysis-syndrome-prevention-and-treatment.
3. Venetoclax. Monograph. Clinical Pharmacology [database online].

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Supplemental Information:

Table 1: Recommended TLS Prophylaxis Based on Tumor Burden in Patients with CLL/SLL

Tumor Burden	Anti-hyperuricemics	Hydration	Lab Monitoring
Low Tumor Burden			
All lymph nodes <5 cm **and** ALC <25x10^9/L	Allopurinol Start 2-3 days prior to first dose	Oral (1.5-2 L/day) beginning 2-3 days prior to first dose	Outpatient: First dose of 20 mg and 50 mg: Pre-dose, 6-8 hrs and 24 hrs Subsequent ramp up doses: Pre-dose only
Medium Tumor Burden			
Any lymph node 5cm to <10 cm **or** ALC ≥ 25 x 10^9/L	Allopurinol Start 2-3 days prior to first dose	Oral (1.5-2L/day) beginning 2-3 days prior to first dose Consider additional IV if in hospital	Outpatient: First dose of 20 mg and 50 mg: Pre-dose, 6-8 hrs and 24 hrs Subsequent ramp up doses: Pre-dose only **If CrCl<80 ml/min** consider hospitalization and follow lab monitoring for inpatient below
High Tumor Burden			
Any lymph node ≥ 10 cm **or** Any lymph node ≥ 5 cm **and** ALC ≥ 25x 10^9/L	Allopurinol Start 2-3 days prior to first dose Consider rasburicase if elevated baseline uric acid Check with inpatient pharmacy for availability	Oral (1.5-2 L/day) beginning 2-3 days prior to first dose and IV (150- 200 mL/hr as tolerated)	In hospital: For first dose of 20 mg and 50 mg: Pre-dose, 4 ,8 ,12 and 24 hrs Outpatient:For subsequent ramp-up doses: Pre-dose, 6-8 hrs and 24 hrs

Important Drug safety information:

- S*trong* CYP3A - *contraindicated during ramp up phase* in CLL/SLL due to increased risk of TLS
- Avoid grapefruit products, Seville oranges, and starfruit (all CYP3A inhibitors)
- If a *strong* CYP3A inhibitor must be used, patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax reduce venetoclax by at least **75%**.
  - Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2-3 days after discontinuation of the inhibitor
- If a *moderate* CYP3A inhibitors or P-gp inhibitor must be used, reduce the venetoclax dose by *at least* **50%**. Monitor patients more closely for signs of venetoclax toxicities. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.