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Positive Quality Intervention: Venetoclax (Venclexta®) Use in Chronic Lymphocytic Leukemia

Description: Dose adjustments for drug-drug interactions and adverse events, tumor lysis syndrome (TLS) risk assessment, prophylaxis and monitoring are important components of venetoclax management.[1] Depending on a patient's risk for tumor lysis syndrome (TLS), some patients may require hospital admission during the dose titration process.[2] The hospital admission presents its own set of challenges and effective communication between the oncology pharmacist, nurse, lab technicians, hematologist, and the patient is necessary to make sure the recommended administration guidelines and lab monitoring are followed and ensure patient safety and best outcomes.

Background: B-cell lymphoma 2 (BCL2) is an antiapoptotic protein which is overexpressed in CLL/SLL. Venetoclax is a BCL2 inhibitor and has been used in combination with obinutuzumab or rituximab in the treatment of CLL/SLL.[1] The phase 3 Murano trial showed a higher rate of 2-year PFS in relapsed or refractory CLL patients treated with venetoclax-rituximab vs. bendamustine-rituximab 83% vs 39% (HR=0.19 95% CI, 0.13-0.28; P<0.0001) including patients with del (17p)/TP53 mutation. [3] The CLL14 Phase 3 trial evaluated the efficacy and safety of 12 month fixed treatment duration venetoclax-obinutuzumab vs chlorambucil-obinutuzumab in treatment naïve patients with CLL/SLL with comorbidities. Venetoclax-obinutuzumab fixed treatment duration regimen significantly improved progression-free survival compared to the chlorambucil-obinutuzumab (HR=0.33, 0.22-0.51, p<0.0001). PFS benefit of Venetoclax-obinutuzumab was also shown in pre-specified clinical subgroups including patients with del (17p)TP53 mutation.[4] Three months after treatment completion, a greater percentage of patients on venetoclax-obinutuzumab vs chlorambucil-obinutuzumab achieved minimal residual disease in peripheral blood and bone marrow.[5] Additionally at 5-year follow up and after being off treatment for 4 years, 72% of patients treated with venetoclax-obinutuzumab have not received subsequent therapy vs 43% of patients treated with chlorambicil-obinutuzumab.[6]

PQI Process: Upon receipt of a new prescription for venetoclax:[1,2]

- Determine if the prescriber has assigned a TLS risk category for the patient (see supplemental information and the **TLS Risk Assessment Tool**)
- 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
        - Most prescriptions will require a prior authorization which may cause delays.
    - Coordinate with inpatient team the 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 that the labs are not seen as "duplicates" and inadvertently cancelled
        - Labs need to be reviewed in "real time" for early detection of TLS
    - In select patients, rasburicase may be used for TLS management
        - See **Use of Rasburicase (Elitek®) for Treatment of Tumor Lysis Syndrome** PQI
- Screen for drug-drug interactions (see **Dose Modification Charts for Venetoclax Treatment Tool**)

Dosing Guideline: Assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperurecemics to patients prior to first dose and throughout the ramp-up phase. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.

Venetoclax-Obinutuzumab Dosing:
The venetoclax + obinutuzumab regimen is designed to be completed after 12 months (a total of twelve 28-day treatment cycles) obinutuzumab is administered in cycles 1-6 and venetoclax is administered for a total of 12 cycles.

- Start obinutuzumab administration on Cycle 1, Day 1: 100 mg on Cycle 1 Day 1 followed by 900 mg on Cycle 1 Day 2. Administer 1000 mg on Cycle 1, Day 8 and Cycle 1, Day 15. Follow by administering 1000 mg of obinutuzumab on Day 1 of each subsequent cycle (Cycles 2-6).
- Start venetoclax on Cycle 1 Day 22 according to 5-week ramp up schedule. After completing 4 weeks of the ramp up phase (on Cycle 2 Day 28), continue venetoclax at 400 mg daily starting on Cycle 3, Day 1 through Cycle 12.

Venetoclax-Rituximab Dosing:
The venetoclax + rituximab regimen is designed to be completed after 24 months (twenty-four 28-day treatment cycles) after completing the 5-week venetoclax dose ramp-up:[1]

- Start venetoclax ramp up according to 5-week ramp up schedule. Venetoclax is taken at 400mg once daily from Cycle 1 Day 1 of rituximab through Cycle 24.
- Rituximab is administered at 375 mg/m^2 on Day 1, Cycle 1 and 500 mg/m^2 on Day 1, Cycles 2-6. Cycle 1 starts after completion of venetoclax 5 week ramp up.

Venetoclax Ramp-Up Schedule[1]

Week 1	20 mg	The 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
Week 2	50 mg	
Week 3	100 mg	
Week 4	200 mg	
Week 5 and beyond	400 mg	

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 and ensure it is 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. Seymour, John F., et al. "Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia." *New England Journal of Medicine* 378.12 (2018): 1107-1120.
4. Fischer, Kirsten, et al. "Venetoclax and obinutuzumab in patients with CLL and coexisting conditions." *New England Journal of Medicine* 380.23 (2019): 2225-2236.
5. Al-Sawaf, Othman, et al. "Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study." *Journal of Clinical Oncology* 39.36 (2021): 4049-4060.
6. Al-Sawaf et.al EHA 2022 Abstract S148; Seymour JF Blood 2022.

Supplemental Information:

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

Tumor Burden	Anti-hyperurecemics	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 Inhibitors- *contraindicated during ramp up phase* in CLL 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.