

Positive Quality Intervention: Venetoclax Risk Stratification, Dosing, and Dispensing Procedure

Description:

Venetoclax is a selective inhibitor of B cell lymphoma-2 (BCL-2). Inhibition of BCL-2 by venetoclax results in cytotoxic activity in tumor cells that overexpress BCL-2 by restoring apoptosis. 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). 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:

TLS can occur when there is large tumor burden (large size of any lymph node, or, elevated Absolute Lymphocyte Count (ALC). Cell lysis can release large amounts of potassium, phosphate and uric acid into systemic circulation. Elevated potassium may put the patient at risk for cardiac arrhythmias, and the resulting hyperphosphatemia and hyperuricemia may lead to the formation of calcium phosphate and uric acid precipitates in the renal tubules, which may result in renal failure. 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 3% 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.
- Confirm patient's risk for TLS based on current labs and verify that they have been assigned to the appropriate risk category. Refer to table 1 for recommendations on titration in the outpatient/in-hospital setting and monitoring in CLL/SLL patients.
- If patient falls into the high TLS risk category (or medium risk with CrCl<80ml/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 per Table 1.
 - Labs will need to be ordered for the first dose of 20mg and 50mg doses. This will occur on two separate admissions.
 - Labs need to be drawn pre-dose, 4, 8, 12 and 24 hours after the dose.

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- 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 (e.g., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase (LDH) levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing VENCLEXTA 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 10⁹/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. Ensure staff is familiar with policies and that drug supply is available. Dosing of rasburicase may vary per institutional policies (ie. weight based vs flat dosing)

Dosing Guideline:

For all indications assess patient-specific factors for level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemics to patients prior to first dose of VENCLEXTA and throughout the ramp-up phase to reduce risk of TLS.

Venetoclax Ramp-Up Schedule

CLL/SLL [§]		AML		[§] The CLL/SLL Starting Pack provides the first 4 weeks of VENCLEXTA according to the ramp-up schedule. The 400 mg dose is achieved using 4 x 100 mg tablets supplied in bottles. *400mg when used in combination with azacitidine or decitabine; 600mg when used in combination with low dose cytarabine
Week 1	20 mg daily	Day 1	100 mg	
Week 2	50 mg daily	Day 2	200 mg	
Week 3	100 mg daily	Day 3	400 mg	
Week 4	200 mg daily	Day 4 and beyond	400 mg or 600 mg*	
Week 5 and beyond	400 mg daily			

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Important Drug safety information:

- *Strong* CYP3A inhibitors interact with venetoclax; concomitant use is *contraindicated during the ramp up phase* in CLL/SLL due to the increased risk of tumor lysis syndrome.
- Avoid grapefruit products, Seville oranges, and starfruit (all CYP3A inhibitors) during treatment with venetoclax.
- 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 may reduce the dose by at least **75%** when used concomitantly with strong CYP3A inhibitors. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 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.

Patient Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) Sheet
- Review titration schedule with patient
- 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 the missed dose is within 8 hours of the usual time patient should take as soon as possible and then resume their normal schedule
 - If the missed dose is greater than 8 hours the patient should skip the missed dose and resume their normal schedule the following day.
- For patients identified as having medium tumor burden with poor renal function or high tumor burden: confirm with the patient the date, time, and location of hospital should the provider deem admission is necessary.
- Consider providing a calendar with dosing schedule and lab appointments.
- Follow up with patient after each dose escalation to confirm patient is taking medications properly.

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References:

1. VENCLEXTA® (Venetoclax) [Prescribing Information]. Chicago, IL: AbbVie, Inc., February 2018
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SUPPLEMENTAL INFORMATION:

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

Tumor Burden Classification	Anti-hyperuricemics	Hydration	Lab Monitoring
Low Tumor Burden			
All lymph nodes <5cm and ALC <25x10 ⁹ /L	Allopurinol Start 2-3 days prior to first dose	Oral (1.5-2L/day) beginning 2-3 days prior to first dose	Outpatient: First dose of 20mg and 50mg: Pre-dose, 6-8 hrs and 24 hrs. Subsequent ramp up doses: Pre-dose only.
Medium Tumor Burden			
Any lymph node 5cm to <10cm 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 20mg and 50mg: 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 >= 10cm or Any lymph node >= 5cm and ALC>= 25x 10 ⁹ /L	Allopurinol Start 2-3 days prior to first dose Consider Rasburicase if patient has elevated baseline uric acid. Check with inpatient pharmacy to see if available.	Oral (1.5-2L/day) beginning 2-3 days prior to first dose and IV (150-200 ml/hr as tolerated)	In hospital: For first dose of 20mg and 50mg: Pre-dose, 4 ,8 ,12 and 24 hrs Outpatient: For subsequent ramp-up doses: Pre-dose, 6-8 hrs and 24 hrs.

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