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Positive Quality Intervention: Acalabrutinib (Calquence®) In Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Description: The purpose of this PQI is to discuss the clinical considerations around the use of acalabrutinib (Calquence®) to optimize the outcomes for patients with CLL/SLL.

Background: Acalabrutinib is a Bruton tyrosine kinase (BTK) inhibitor initially indicated for mantle cell lymphoma (MCL) patients who have received one prior therapy. In late 2019, it received an indication for the treatment of CLL/SLL either as monotherapy or in combination with obinutuzumab.[1]
Efficacy in the front-line setting was established by the ELEVATE-TN trial, demonstrating progression-free survival advantage of acalabrutinib when administered with or without obinutuzumab, when compared to obinutuzumab plus chlorambucil.[2] At a median follow up of 28.3 months, acalabrutinib plus obinutuzumab improved PFS and ORR compared with obinutuzumab plus chlorambucil in the ELEVATE-TN trial (ORR 93% vs. 78.5%, PFS 93% vs. 47% respectively).[2]
The ASCEND trial displayed advantage in progression-free survival of acalabrutinib monotherapy in the relapsed/refractory setting when matched against investigator's choice of rituximab product plus idelalisib or bendamustine.[3] As monotherapy, acalabrutinib significantly improved PFS, but not ORR, in both the ELEVATE-TN and in the ASCEND trial. ELEVATE-TN trial ORR: 85% vs. 78.5%, ASCEND trial ORR: 80% monotherapy vs. 84% idelalisib plus rituximab (I-R) or bendamustine plus rituximab (B-R); ASCEND trial PFS: not reached in monotherapy vs. 16.5 months for the I-R/B-R arm.[3]
In ELEVATE-RR, the trial that put acalabrutinib head-to-head with ibrutinib as monotherapies, the primary endpoint concluded that acalabrutinib had a non-inferior PFS compared to ibrutinib. In addition, acalabrutinib had less cardiotoxicity and was discontinued less due to adverse events.[4] At a median follow up of 41 months, acalabrutinib had a PFS of 38.4 months compared 38.4 months with ibrutinib. Acalabrutinib displayed less atrial fibrillation incidence than ibrutinib (9.4% vs 16.0%), less hypertension (9% vs 23%), and was discontinued less due to adverse events (15% vs 22%).

PQI Process:
Upon the receipt of a new prescription of acalabrutinib for CLL/SLL:

- Verify dosage: the recommended starting dose of acalabrutinib is 100 mg every 12 hours, taken whole with water and with or without food
    - If dose is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time
    - Avoid in severe hepatic impairment
    - No dose adjustment needed in mild to moderate hepatic or renal impairment (use in severe renal impairment or with dialysis has not yet been evaluated
- Review patient medication list for possible drug-drug interactions
    - Strong CYP3A4 inducer: if use cannot be avoided increase dosage to 200 mg every 12 hours

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  - Strong CYP3A4 inhibitor: avoid use, but if the inhibitor is a short-term medication, stop acalabrutinib and resume after inhibitor is complete
  - Taken with moderate CYP3A4 inhibitor: reduce dosage to 100 mg daily
- Acalabrutinib should be avoided with proton pump inhibitors
  - If other gastric reducing agents are used, recommend taking acalabrutinib 2 hours prior to taking a H2 receptor antagonist, if using an antacid separate dosing by at least 2 hours
- In combination with obinutuzumab, acalabrutinib should be taken **BEFORE** the obinutuzumab

Adverse Events and Management[1]

Category	Occurrence	Action
Fatal and serious infections, including opportunistic infections	Serious or Grade 3 or higher infections (bacterial, viral, or fungal) occurred in 19% of 1029 patients in clinical trials	Consider prophylaxis in patients who are at increased risk for opportunistic infections. Monitor for signs and symptoms of infection and treat promptly
Fatal and serious hemorrhagic events	Major hemorrhage (serious or Grade 3 or higher bleeding or any central nervous system bleeding) occurred in 3.0% of patients, with fatal hemorrhage occurring in 0.1% of 1029 patients in clinical trials. Bleeding events of any grade, excluding bruising and petechiae, occurred in 22% of patients	Monitor patients for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre-and post-surgery depending on type of surgery and the risk of bleeding Caution in patients on antithrombotic agents
Grade 3 or 4 Cytopenias	Neutropenia (23%), anemia (8%), thrombocytopenia (7%), and lymphopenia (7%), developed in patients. Grade 4 neutropenia developed in 12% of patients	Monitor complete blood counts regularly during treatment. Interrupt treatment, reduce the dose, or discontinue treatment as warranted
Cardiac Factors	Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection	Monitor for symptoms of arrhythmia (ex. palpitations, dizziness, syncope, dyspnea) and manage as appropriate
Skin Cancer	The most frequent second primary malignancy was skin cancer, reported in 6% of patients	Monitor patients for skin cancers and advise protection from sun exposure

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Dose Modifications[1]

Event	Event Occurrence	Dose Modification (Starting dose = 100 mg every 12 hours)
Grade 3 or greater non-hematologic toxicities Grade 3 thrombocytopenia with bleeding Grade 4 thrombocytopenia Grade 4 neutropenia lasting longer than 7 days	First and Second	Interrupt acalabrutinib Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at 100mg approximately every 12 hours
	Third	Interrupt acalabrutinib Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at a reduced frequency of 100 mg daily
	Fourth	Discontinue acalabrutinib

Patient Centered Activities:

- Patient Education
  - Provide Oncology Chemotherapy Education (OCE) sheet and review with patient
  - Instruct patient to report any signs or symptoms of atrial fibrillation or flutter such as palpitations, dizziness, faint, chest discomfort
  - Patient should be made aware of the increased bleeding risk associated with acalabrutinib
    - Due to this risk, they may need to hold their medication prior to any procedures
  - Ensure patient has access to supportive medications for diarrhea such as loperamide
- AstraZeneca Access 360® Program
  - Calquence® Co-Pay Savings Program (commercially insured patients)
  - AZ&Me Prescription Savings Program
    - Provides AstraZeneca medicines at no cost to qualifying patients
  - Patient Assistance foundations (federally insured patients)
- CALQUENCECares®
  - Service through AstraZeneca to provide education and support during treatment

References:

1. Calquence® (acalabrutinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP.
2. Sharman JP, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukemia (ELEVATE TN): a randomized, controlled, phase 3 trial. *Lancet.* 2020 Apr 18;395(10232):1278-1291.
3. Ghia P, et al. ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol.* 2020;