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Positive Quality Intervention: Ibrutinib Dose Optimization

Description: This document will review ibrutinib, with a particular focus on the appropriate dose modifications required to manage adverse effects.

Background: Ibrutinib, marketed under the brand name Imbruvica®, is a Bruton's tyrosine kinase (BTK) inhibitor utilized in the treatment of various B-cell malignancies, with FDA labeled indications for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Waldenström macroglobulinemia as well as chronic graft versus host disease (cGVHD).[1] It is also used off label for the treatment of mantle cell lymphoma.[2] By inhibiting the BTK protein, ibrutinib impedes the growth and survival of malignant B-cells, which is essential to slow or halt disease progression.[1]

The standard starting adult dose for ibrutinib is 420 mg and is consistent across all FDA approved indications. Despite its efficacy, dose adjustments may be required to manage adverse effects and optimize patient outcomes. Common adverse events include diarrhea, fatigue, musculoskeletal pain, neutropenia, hypertension and infections. More severe adverse effects including bleeding, cardiac arrhythmias, and atrial fibrillation are also possible. Additionally, ibrutinib is a minor substrate of CYP2D6 and a major substrate of CYP 3A4; therefore, monitoring for potential drug-drug interactions and considering dose adjustments are necessary when utilizing this medication.

PQI Process: Upon receiving a new ibrutinib prescription:

- Review patient history for heart failure, QTc prolongation or uncontrolled hypertension.
- Review current medications and check for drug-drug interactions
  - Review current labs for tumor lysis syndrome risk and ensure hepatitis B testing has been completed
  - Confirm appropriate indication and dosing (FDA labeled indications below)
    - CLL/SLL 420 mg once daily
      - Hepatic Impairment: 140 mg for Child-Pugh Class A and 70 mg for Child-Pugh Class B
    - Waldenstrom macroglobulinemia 420 mg once daily
      - Hepatic Impairment: 140 mg for Child-Pugh Class A and 70 mg for Child-Pugh Class B
    - cGVHD 420 mg once daily
      - Hepatic Impairment: If bilirubin is >1.5 to 3 x upper limit of normal, the recommended dose is 140 mg for patients 12 years and older
- Verify which dosage form of ibrutinib is being prescribed – tablet, capsule, or oral suspension
- Monitoring Parameters:
    - CBC with differential, metabolic panel, uric acid levels at baseline and as clinically indicated
    - ECG at baseline and as clinically indicated
    - Consider PJP prophylaxis with sulfamethoxazole or atovaquone
    - Consider VZV prophylaxis with acyclovir or valacyclovir
    - Consider antifungal prophylaxis as indicated during periods of neutropenia
    - Monitor complete blood counts monthly and consider use of growth factor support as indicated
    - Evaluate bilirubin and liver transaminases at baseline and throughout treatment course

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Insights into Adverse Reactions (ARs) and Dose Optimization

Recommended Ibrutinib Dosage Modifications for Adverse Reactions[1]

AR	1st Occurrence	2nd Occurrence	3rd Occurrence
Cardiac			
Grade 2 cardiac failure	Restart at 280 mg daily	Restart at 140 mg daily	Discontinue
Grade 3 cardiac arrhythmias	Restart at 280 mg daily	Discontinue	
Grade 3 or cardiac failure	Discontinue		
Grade 4 cardiac arrhythmia	Discontinue		
Non-Cardiac			
Grade 3 or 4 other non-hematologic toxicities	Restart at 280 mg daily	Restart at 140 mg daily	Discontinue
Grade 3 or 4 neutropenia with infection or fever	Restart at 280 mg daily	Restart at 140 mg daily	Discontinue
Grade 4 hematologic toxicities	Restart at 280 mg daily	Restart at 140 mg daily	Discontinue

The RESONATE-2 trial studied ibrutinib versus chlorambucil in patients with newly diagnosed CLL. Long term follow-up data, up to 8 years in some patients, is available.[3]

Adverse reactions of clinical interest reported from 8-year follow-up of RESONATE-2[3,4]:

ARs (all grades) occurring in ≥ 20% of patients receiving ibrutinib (n = 135)	
AR	**All grades (%)**
Diarrhea	50
Cough	37
Fatigue	37
Arthralgia	32
Nausea	31

ARs (grade 3) occurring in > 5% of patients receiving ibrutinib (n = 135)	
AR	**Grade 3 (%)**
Hypertension	12
Major hemorrhage	7
Atrial fibrillation	6

ARs cited as the primary reason for discontinuation of ibrutinib in RESONATE-2 long term follow-up data were atrial fibrillation, pneumonia, and palpitations. Discontinuation rates were highest in the initial years of treatment and decreased over time. For patients who discontinued ibrutinib because of ARs (n = 32), OS estimate rate at 7 years from the time of randomization was 60%. Primary reasons for dose reductions were thrombocytopenia, anemia, arthralgia, diarrhea, fatigue and palpitations. A 7-year PFS rate of 59% was seen in patients with and without AR-necessitated ibrutinib dose reductions.[3,4]

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Rationale for Dose Reductions

Dose reductions are indicated when patients experience moderate to severe adverse effects or persistent symptoms despite optimal supportive care. The primary objectives are to maintain therapeutic efficacy and enhance patient tolerability. Key reasons for dose reduction include:

- Managing Toxicity: Dose reduction can mitigate adverse effects, thereby improving patient tolerability and compliance.
- Improving Adherence: Lowering the dose may facilitate better adherence to the treatment regimen, ensuring sustained therapeutic efficacy.
- Personalized Medicine: Individualizing the dose based on patient response and tolerance can lead to improved clinical outcomes.

Multidisciplinary, Patient Centered Approach

Engaging a multidisciplinary team, including oncologists, pharmacists, and nurses, to determine the most appropriate course of action.

- Collaborate with the patient:
  - Involve patients in discussions about dose reductions, side effects, and the reasoning behind any potential changes
- Comprehensive assessment:
  - Take into consideration patient feedback, i.e. concerns regarding quality of life, anxiety related to toxicities, management of toxicities, etc.
  - Consider patient comorbidities
  - Regular review of labs to monitor infection, hepatotoxicity, etc.
  - Cardiovascular monitoring of risk factors with appropriate diagnostic testing as indicated
  - Upcoming surgical procedures that may require holding the ibrutinib dose – typically 3-7 days before and after procedures
- Proactive side effect management:
  - Preventative care: for predictable adverse reactions like neutropenia, preemptive use of growth factors or infection prophylaxis could be considered as it may reduce treatment interruptions.
  - Supportive therapies: incorporate interventions such as beta-blockers for cardiac management or anti-infective medications for neutropenic patients
  - Close monitoring: use regular lab testing and clinical follow-ups to detect toxicity early, allowing for timely adjustments.
- Emotional support:
  - Utilize all members of the care team that have built trusting relationships with the patients to offer empathy, reassurance and evidence-based guidance.

References:

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