National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

Written By: Jody Agena, PharmD, MBA, BCOP
Virginia Cancer Specialists
Last Update 1/11/19

Positive Quality Intervention: Ibrutinib Management

Description:

Ibrutinib is a small molecule that acts as a potent, irreversible inhibitor of Bruton's Tyrosine Kinase (BTK), a key component of the B-Cell receptor and cytokine receptor pathway. BTK inhibition is vital for decreased malignant B-Cell proliferation and survival. This molecule disrupts the proliferation of B-Cell cancers such as Mantle Cell Lymphoma, Chronic/Small Lymphocytic Leukemia, Marginal Zone Lymphoma, and Waldenstrom Macroglobulinemia. Managing both medication dosing and adverse effects are prime examples of key areas for additional intervention opportunities for improved patient health outcomes within the medically integrated team.

Background:

Dosing of ibrutinib varies by disease/indication and should be carefully assessed. Although the dose may stabilize over time, drug interactions frequently occur with common anti-infective agents. Lymphocytosis is a noted adverse effect of ibrutinib which results in an increased count of lymphocytes in the blood; a common and expected occurrence which does not reflect progression of the disease. Monitoring patient laboratory values must be considered and evaluated based on patient need.

PQI Process:

Upon receiving new ibrutinib prescription:

- Confirm appropriate dosing and indication.
- Monitor CBC at baseline, monthly and as clinically necessary
- Monitor CMP, Uric Acid Levels at baseline, monthly and as clinically necessary
- ECG at baseline (positive cardiac history/ risk factors) and periodically as necessary
- Evaluate patients on anticoagulation, including aspirin, for bleeding risk. The use of anticoagulation with ibrutinib should be assessed with each patient based on risk versus benefit. It is recommended to withhold treatment 3 days pre/post minor surgical procedures and pre/post 7 days for major surgical procedures
- Consider Pneumocystis jirovecii Pneumonia (PJP) prophylaxis in patients with increased risk of opportunistic infections
- Lymphocytosis: Upon initiation of Ibrutinib, lymphocytosis commonly occurs in first weeks and resolves by week 8 of therapy; does not reflect disease progression
- Monitor for drug interactions, adherence, and adverse effects

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Dosing Guidelines*

Indication	Dose (Daily)	Efficacy
CLL	420 mg	*Byrd et al.*, 2014[2]
Mantle Cell Lymphoma	560 mg	*Wang et al.*, 2015[4]
Marginal Zone Lymphoma	560 mg	*Noy et al.*, 2017[3]
Waldenstrom Macroglobulinemia	420 mg	*Dimopoulos et al.*, 2018[1]
Chronic GVHD	420 mg	*Miklos et al.*, 2016[5]

*Ibrutinib dosing may vary with combination therapies and with drug interactions.

Adverse Effects

Adverse Reaction	All Grades (%)
Diarrhea	51
Fatigue	41
Musculoskeletal Pain	37
Peripheral Edema	35
Respiratory Tract Infection	34
Nausea	31
Bruising	30

Adverse Reaction	Grades ≥3 (%)
Hemorrhage	6
Infections	29
Cytopenias	13-39
Cardiac Arrhythmia	6
Secondary Malignancies	16
Hypertension	17

Recommended Dose Modifications for Toxicity

Toxicity Occurrence	MCL and MZL After Recovery Starting Dose = 560 mg	CLL/SLL, WM, and cGVHD After Recovery Starting Dose = 420 mg
First	Restart at 560 mg daily	Restart at 420 mg daily
Second	Restart at 420 mg daily	Restart at 280 mg daily
Third	Restart at 280 mg daily	Restart at 140 mg daily
Fourth	Discontinue	Discontinue

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Patient Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) sheet
- Ensure patients understand the formulation prescribed and how to take their dose.
    - Varying Dosage Forms: capsules - 70 mg, 140 mg; tablets - 140 mg, 280 mg, 420 mg, 560 mg
- Administer orally once daily with a glass of water
- Swallow capsules whole; do not break, crush, chew
- If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day
- Proper sign/symptom monitoring
    - Abnormal bruising or bleeding especially those on anticoagulation or aspirin
    - GI tolerance issues (nausea, vomiting, diarrhea, etc.)
    - Any new medications (assess for risk of QT prolongation or other drug-drug interactions, particularly with acute anti-infective drugs, with potential for holding or lowering ibrutinib dose during certain required treatments)
- Evaluate if patients have missed any doses between cycles to determine if interventions are needed such as reminders, calendars, pill boxes, etc.

Drug Interactions:

- CYP3A4 Inducers (Strong): May decrease the serum concentration of Ibrutinib. (e.g. Carbamazepine, rifampin, phenytoin, St. John's Wort) Risk: Avoid combination
- CYP3A4 Inhibitors (Strong): May increase the serum concentration of Ibrutinib. Management: Avoid concomitant use of ibrutinib and strong CYP3A4 inhibitors. If a strong CYP3A4 inhibitor must be used short-term (eg, anti-infectives for 7 days or less), interrupt ibrutinib therapy until the strong CYP3A4 inhibitor is discontinued (e.g. Ketoconozole, Itraconazole, voriconazole, Posaconazole, Clarithromycin, Telithromycin). Risk: Avoid combination
- Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. Risk: Avoid combination
- Warfarin and anticoagulation: increased bleeding risk: Consider risk versus benefit.
    - Secondary analysis of RESONATE trial and Phase I study participants on anticoagulation and ibrutinib - Among 175 patients receiving concomitant anticoagulant or antiplatelet agents, 5 had major bleeding events (3%), and Grade 1 bleed in occurred in 10-20%. These events were typically observed in conjunction with other factors, such as coexisting medical conditions and/or concurrent medications.[6]

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6. Jones JA, Hillmen P, Coutre S, et al. Use of anticoagulants and antiplatelet in patients with chronic lymphocytic leukaemia treated with single-agent ibrutinib. *Br J Haematol*. 2017;178(2):286-291.