Written By: Jody Agena, PharmD, MBA, BCOP
Virginia Cancer Specialists

Positive Quality Intervention: Ibrutinib (Imbruvica®) Management

Description: This document will review the appropriate management and clinical interventions with ibrutinib.

Background: 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 signaling pathway. BTK inhibition is vital for decreased malignant B-cell proliferation and survival. This molecule disrupts the proliferation of B-cell cancers such as Chronic/Small Lymphocytic Leukemia (CLL/SLL), Waldenström's Macroglobulinemia (WM), and chronic Graft Versus Host Disease (cGVHD). Management of 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.[1-6]

PQI Process: Upon receiving new ibrutinib prescription:

- Confirm appropriate indication and dosing:
  - CLL/SLL 420 mg by mouth once daily
  - Waldenstroms Macroglobulinemia 420 mg by mouth once daily
  - cGVHD 420 mg (>12 yo) or 240 mg/m^2 (1-12 yo) by mouth once daily
- Monitor CBC at baseline, monthly and as clinically necessary
- Monitor CMP, uric acid levels at baseline, monthly and as clinically necessary
- ECG at baseline (patients with cardiac history/risk factors) and periodically as clinically necessary
- Evaluate patients on anticoagulation, including low-dose aspirin, for bleeding risk
- Hold 3 days pre/post minor surgical procedures and pre/post 7 days for major surgical procedures
- Consider Pneumocystis Jirovecii Pneumonia (PJP) prophylaxis
- Lymphocytosis commonly occurs in first weeks and resolves by week 8 (median) of therapy *Does not reflect disease progression*

Adverse Effects

Adverse Reaction	All Grades (%)
Diarrhea	51
Fatigue	41
Musculoskeletal Pain	37
Peripheral Edema	35
Upper Respiratory Tract Infection	34
Nausea	31
Bruising	30
Secondary Malignancies	16

Adverse Reaction	Grade ≥3 (%)
Hemorrhage	6
Infections	29
Cytopenias	13-39
Cardiac Arrhythmia	6
Hypertension	17

Recommended Dose Modifications for Toxicity Occurrences:

Adverse Reaction	Occurrence	Dose Modification MCL/MZL After Recovery	Dose Modification CLL/SLL, WM, cGVHD (>12 yo) After Recovery	Dose Modification cGVHD (1-12 yo) After Recovery
Grade 3 Cardiac Arrhythmias	First	Restart at 420 mg daily	Restart at 280 mg daily	Restart at 160 mg/m^2 daily
	Second	Discontinue	Discontinue	Discontinue
Grade 3/4 Cardiac Failure, Grade 4 Cardiac Arrythmia	First	Discontinue	Discontinue	Discontinue
Grade 2 Cardiac Failure, Other Grade 3/4 Non-Hematological Toxicity, Grade 3/4 Neutropenia with Infection/Fever, Grade 4 Hematologic Toxicity	First	Restart at 420 mg daily	Restart at 280 mg daily	Restart at 160 mg/m^2 daily
	Second	Restart at 280 mg daily	Restart at 140 mg daily	Restart at 80 mg/m^2 daily
	Third	Discontinue	Discontinue	Discontinue

Drug Interactions:

- CYP3A4 Inducers (Strong): May decrease the serum concentration of ibrutinib. (ex. 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 (ex. anti-infectives for 7 days or less), interrupt ibrutinib therapy until the strong CYP3A4 inhibitor is discontinued (ex. ketoconozole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin). Risk: Avoid combination
- Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of vaccines. Immunosuppressants may diminish the therapeutic effect of vaccines. 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 showed that 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]

Patient-Centered Activities:

- Provide Oral 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, 70 mg/mL (108 mL)

- Administer orally once daily with a glass of water
- Swallow whole; do not break, crush, chew with tablets and capsules
- 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
    - If any abnormal bruising or bleeding especially those on anticoagulation or aspirin
    - If there are any new medications (assess for risk of QT prolongation or drug-drug interactions)
    - Evaluate if patients have missed any doses between cycles to determine if interventions are needed such as reminders, calendars, pill boxes, etc
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Dimopoulos MA, Tedeschi A, Trotman J, et al; iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. *N Engl J Med*. 2018;378(25):2399-2410.
2. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371(3):213-223.
3. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126(6):739-745.
4. Miklos D, Cutler CS, Arora M, et al. Multicenter open-label phase 2 study of ibrutinib in chronic graft versus host disease (cGVHD) after failure of corticosteroids. *Blood*. 2016;128(22).
5. 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.
6. Imbruvica® (ibrutinib) [package insert].