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Positive Quality Intervention: Ibrutinib (Imbruvica®) Management in Pediatric Patients

Description: This document will review the appropriate management and clinical interventions with ibrutinib for pediatric patients with chronic Graft Versus Host Disease (cGVHD).

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 B-cell surface receptor activation. By disrupting these pathways, ibrutinib is able to treat cGVHD after failure of one or more lines of systemic therapy. The iMAGINE study evaluated the PK, safety, and efficacy of ibrutinib in patients ≥ 1 to 22 years old with treatment-naïve (TN) or relapsed/refractory (R/R) moderate/severe cGVHD. Plasma concentration-time profiles for ibrutinib 240 mg/m^2 (recommended pediatric equivalent) were comparable to those observed in adults with cGVHD at a dose of 420 mg/day. Safety was consistent with the known profile of ibrutinib in cGVHD. The overall response rate by 24 weeks was 64%, including 83% for the TN subgroup and 60% for R/R. Among 46 responders (median follow-up, 20 months; range, 2 to 32 months), 12- month duration of response for each subgroup was 60% (95% confidence interval (CI), 25% to 83%) in TN patients and 58% (95% CI, 35% to 75%) in R/R patients.[1] 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.

PQI Process: Upon receiving new ibrutinib prescription in pediatric patients

- Confirm appropriate indication and dosing
  cGVHD 420 mg (>12 yo) or 240 mg/m^2 (1-12 yo) by mouth once daily (max 420 mg)

	Recommended dose to achieve 240 mg/m^2	
BSA (m^2) Range	Dose (mg) Capsules/Tablets	Dose (mL) Oral Suspension (70 mg/mL)
> 0.3 to 0.4	-	1.2 mL
> 0.4 to 0.5	-	1.5 mL
> 0.5 to 0.6	-	1.9 mL
> 0.6 to 0.7	-	2.2 mL
> 0.7 to 0.8	210 mg	2.6 mL
> 0.8 to 0.9	210 mg	2.9 mL
> 0.9 to 1	210 mg	3.3 mL
> 1 to 1.1	280 mg	3.6 mL
> 1.1 to 1.2	280 mg	4 mL
> 1.2 to 1.3	280 mg	4.3 mL
> 1.3 to 1.4	350 mg	4.6 mL
> 1.4 to 1.5	350 mg	5 mL
> 1.5 to 1.6	350 mg	5.3 mL
> 1.6	420 mg	6 mL

- Verify pregnancy status in females of reproductive potential and ensure use of effective contraception during treatment and for 1 month after the last dose
- Monitor CBC at baseline, monthly and as clinically necessary
- Monitor CMP monthly and as clinically necessary
    - Dose modifications are needed in patients with total bilirubin > 1.5-3 x upper limit of normal (unless of non-hepatic origin or due to Gilbert's syndrome)
- Blood pressure and ECG/ECHO 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

Adverse Effects

Adverse Reaction	All Grades (%)
Diarrhea	28
Musculoskeletal Pain	30
Nausea and/or Vomiting	19
Abdominal Pain	23
Bruising	13
Rash	19
Hemorrhage	17
Sinus tachycardia	11

Adverse Reaction	Grade ≥3 (%)
Fever	11
Infections	4-13
Cytopenias	4-13
Hypertension	4
Osteonecrosis	9
Stomatitis	9
Hypokalemia	6
ALT increased	2

Recommended Dose Modifications for Toxicity Occurrences:

Adverse Reaction	Occurrence	cGVHD (>12 yo) After Recovery	Dose Modification cGVHD (1-12 yo) After Recovery
Grade 3 Cardiac Arrhythmias	First	Restart at 280 mg daily*	Restart at 160 mg/m^2 daily*
	Second	Discontinue	Discontinue
Grade 3/4 Cardiac Failure, Grade 4 Cardiac Arrythmia	First	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 280 mg daily*	Restart at 160 mg/m^2 daily*
	Second	Restart at 140 mg daily*	Restart at 80 mg/m^2 daily*
	Third	Discontinue	Discontinue

* Benefit-risk should be evaluated before resuming treatment

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 (e.g. 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)
    - Avoid grapefruit and Seville oranges during ibrutinib treatment
    - Risk: Avoid combination
- Posaconazole and Voriconazole: Dose modifications are recommended based on dose and formulation of the inhibitor
- Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of vaccines and 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

Patient-Centered Activities:

- Provide the attached pediatric patient education 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; suspension: 70 mg/mL (108 mL)
- Administer orally once daily at approximately the same time each day with a glass of water
- Swallow whole; do not break, crush, chew with tablets and capsules
- Suspension
    - With first use document 60 days from opening as the discard date on the container
    - Shake well before use
    - Attached bottle adapter should not be removed and may be wiped with a disposable tissue
    - Use provided oral syringes to measure dose and administer along inside of cheek in the mouth; dose may need to be split between multiple syringes; after use, rinse oral syringe with water only and let air dry
        - If cannot read markings throw away and call 1-877-877-3536 for new syringes
    - Store bottle at 2°C to 25°C (36°F to 77°F)
- 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)
    - Report any signs/symptoms of palpitations, lightheadedness, dizziness, fainting, shortness of breath, chest discomfort, or edema
    - Report any signs/symptoms of infection (fever, chills, weakness, confusion)
    - Evaluate if patients have missed any doses between cycles to determine if interventions are needed such as reminders, calendars, etc
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Carpenter PA, Kang HJ, Yoo KH, et al. Ibrutinib treatment of pediatric chronic graft-versus-host-disease: primary results from the phase ½ iMAGINE study. Transplant Cell Ther 2022; 28(11): 771.e1-771.e10.
2. Imbruvica® (ibrutinib) [package insert].