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Positive Quality Intervention: Ixazomib (Ninlaro®) In the Treatment of Multiple Myeloma

Description: Ixazomib is an oral proteasome inhibitor indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma after at least one prior therapy. This PQI highlights the management, safety, and efficacy of ixazomib.

Background: Multiple Myeloma (MM) is an incurable disease resulting from malignant plasma cells. MM is rare in younger patients (median age at diagnosis 72 years). Patients with MM often experience "CRAB" symptoms defined as hypercalcemia, renal dysfunction, anemia, and bone lesions. Patients generally relapse multiple times and are treated with multi-drug regimens, preferably triplets; common drugs include proteasome inhibitors (PI), immunomodulatory drugs (IMiD), monoclonal antibodies, and steroids.[1] Select patients may be eligible for an autologous stem cell transplant depending on risk factors associated with the disease. For transplant-eligible candidates, Ixazomib may be used in combination with cyclophosphamide and dexamethasone (maybe useful in pts with baseline renal dysfunction).[2] Ixazomib is an oral PI that may be used in the relapsed/refractory (R/R) setting in combination with lenalidomide/dexamethasone. This is an NCCN Category 1 preferred regimen in early relapse (1-3 prior therapies) MM.[3] Off-label considerations include utilizing ixazomib in the front-line setting regardless of transplant eligibility in combination with lenalidomide and dexamethasone or in the r/r setting with pomalidomide/dexamethasone or with dexamethasone alone. Ixazomib provides an all oral treatment option in patients with MM. The most common side effects associated with ixazomib in ≥20% of patients include diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, rash, neutropenia, eye disease, and back pain.

PQI Process:[2] Upon receipt of prescription for ixazomib:

- Prior to therapy initiation, obtain baseline labs CBC/diff, CMP, and relevant MM labs to assess treatment response
    - Select MM labs: lactate dehydrogenase (LDH), beta-2 microglobulin, protein analyses, bone marrow aspirate, and cytogenetic studies
    - Platelet and neutrophils nadir occurs on days 14-21 of each cycle
    - Labs should be monitored monthly but may be more frequent with the first three cycles
- Ensure patients receiving antiviral therapy to prevent herpes zoster reactivation
- Patients on IMiDs (lenalidomide or pomalidomide) should be on aspirin for DVT/PE prophylaxis or therapeutic anticoagulation based on clotting history and risk factors (IMPEDE or SAVED score)
- Patients receiving ixazomib are likely to receive IMiD therapy; ensure REMS requirements are met with IMiD therapy for timely initiation of treatment and to keep cycles on track
- Ixazomib recommended dosing: 4 mg days 1, 8, 15, every 28 days
    - Dose reduce for severe renal impairment or ESRD requiring dialysis and severe hepatic impairment at baseline
        - Baseline CrCl <30 ml/min or ESRD requiring dialysis: 3 mg PO daily on days 1, 8, 15 every 28 days
            - May be given without regard to the timing of dialysis because ixazomib is not dialyzable
        - Baseline total bilirubin >1.5x ULN: 3 mg PO daily on days 1, 8, 15 every 28 days
    - If toxicity occurs during treatment, ixazomib should be held and dose reduced to the next lower dose if attributed to therapy
    - Ixazomib is available as 4 mg, 3 mg, and 2.3 mg allowing for 25% incremental dose adjustments
- Avoid concomitant administration of ixazomib with strong CYP3A inducers

Alternating Dose Reductions with Lenalidomide			
Reaction	Platelets	Neutrophils	Rash
Parameter	< 30,000/mm^3	< 500/mm^3	Grade 2 or 3
First Occurrence	Hold ixazomib and lenalidomide Upon recovery, resume both but **reduce lenalidomide** at next lower dose and **continue ixazomib** at most recent dose		
Subsequent Occurrence	Hold ixazomib and lenalidomide Upon recovery, resume both but **reduce ixazomib** at next lower dose and **continue lenalidomide** at most recent dose		

- Monitor for peripheral neuropathy
- It is highly recommended that a therapy calendar be utilized for all patients with MM due to complexity of therapies, older age of patients, and the potential issues if unable to access a medically-integrated pharmacy (eg., triplet-drug regimens may arrive from different sources) (see supplemental information)

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) Sheet and therapy calendar to all patients
- Counsel on the importance of avoiding pregnancy while on treatment and for 90 days after the final dose
- Ensure patients understand the dosing schedule and consider providing a calendar
    - Ixazomib is administered on days 1, 8 and 15 every 28 days
    - Steroid component of regimen may be taken prior to ixazomib to help with nausea control but steroids should be taken with food
    - Ixazomib should be taken on an empty stomach (1 hour before or 2 hours after a meal/snack)
- Advise patients that a missed dose should not be taken within 3 days of the next scheduled dose.
    - If vomiting occurs, do not repeat dose
- Patient Assistance: NCODA Financial Assistance Tool

Supplemental Information

Example 28-Day Dosing Calendar (ixazomib, lenalidomide, dexamethasone)								
	Week 1		**Week 2**		**Week 3**		**Week 4**	
	Day 1	**Days 2-7**	**Day 8**	**Days 9-14**	**Day 15**	**Days 16-21**	**Day 22**	**Days 23-28**
Ixazomib	✓		✓		✓			
Lenalidomide 25 mg	**Take every day on days 1-21**							
Dexamethasone 40 mg	✓		✓		✓		✓	

References:

1. SEER Stat Fact Sheets: Myeloma. Available at http://seer.cancer.gov/statfacts/html/mulmy.html.
2. Ninlaro® (ixazomib) [prescribing information].
3. Kwakman, J. J. M., Elshot, Y. S., Punt, C. J. A., & Koopman, M. (2020, May 13). Management of cytotoxic chemotherapy-induced hand-foot syndrome. Oncology reviews. Retrieved February 23, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7232019/.