National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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Update 5/13/20

Positive Quality Intervention: Ixazomib in the Treatment of Multiple Myeloma

Description:

Ixazomib (Ninlaro) is the only 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 year). Patients with MM often experience "CRAB" symptoms define 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. Select patients may be eligible for an autologous stem cell transplant depending on risk factors associated with disease.

Ixazomib is an oral PI that may be used in the relapsed/refractory (r/r) setting in combination with lenalidomide/dexamethasone. 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. In a clinical phase 1/2 trial, front-line ixazomib/lenalidomide/dexamethasone was associated with a very good partial response in 58% of patients. In the r/r setting, ixazomib-containing regimens demonstrated an improvement in response rates and/or progression free survival. The most common side effects associated with ixazomib in ≥20% of patients include: diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain.

PQI Process:

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
- Ixazomib should be dose reduced for severe renal impairment (or ESRD requiring dialysis), or moderate and severe hepatic impairment at baseline. If toxicity occurs during treatment, ixazomib should be withheld and dose reduced to the next lower dose if attributed to therapy.
    - Baseline CrCl <30 ml/min or ESRD requiring dialysis: 3 mg PO daily on days 1, 8, 15 every 28 days
    - Baseline total bilirubin >1.5x ULN: 3 mg PO daily on days 1, 8, 15 every 28 days
- Ixazomib is metabolized by multiple CYP enzymes and non-CYP proteins. Avoid concomitant administration of ixazomib with strong CYP3A inducers.

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PQI Process continued:

- Ixazomib is available as 4 mg, 3 mg, and 2.3 mg allowing for 25% incremental dose adjustments.

Alternating Dose Reductions with Lenalidomide			
Reaction	Platelets	Neutrophils	Rash
Parameter	< 30,000/mm3	< 500/mm3	Grade 2 or 3
First Occurrence	• Withhold ixazomib and lenalidomide • Upon recovery, resume both but **reduce lenalidomide** at next lower dose and **continue ixazomib** at most recent dose		
Subsequent Occurrence	• Withhold ixazomib and lenalidomide • Upon recovery, resume both but **reduce ixazomib** at next lower dose and **continue lenalidomide** at most recent dose		

***Continue alternating dose reductions for additional occurrences, and review product resources for additional information on managing other adverse events such as peripheral neuropathy**

- Ensure patients receiving PI therapies are also receiving antiviral therapy to prevent against 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.
- Patients receiving ixazomib are likely to receive IMiD therapy. Ensure REMS requirements are met with IMiD therapy for a timely initiation of treatment and to keep cycles on track.
- 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 lack of a medically-integrated pharmacy (i.e. triplet-drug regimens may arrive from different sources). See supplemental index for example.

Patient Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet and therapy calendar to all patients
- Ensure patients understand the dosing schedule. Ixazomib is administered on days 1, 8 and 15 every 28 days. IMiDs and steroids will have a different schedule.
- Advise patients that a missed dose should not be taken with 3 days of the next scheduled dose. If vomiting occurs, do not repeat dose.
    - 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 (at least 1 hour before or 2 hours after a meal or snack.
- Financial resources are available through Takeda Oncology: (https://www.ninlaro.com/cost)

Supplemental Information (if applicable)

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	**Take every day on days 1-21**							
Dexamethasone	✓		✓		✓		✓	

References:

1. Ninlaro (ixazomib) [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Limited; February 2020.
2. SEER Stat Fact Sheets: Myeloma. Available at http://seer.cancer.gov/statfacts/html/mulmy.html. (accessed 04/16/2019)