National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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Positive Quality Intervention: Metastatic Colorectal Cancer- Regorafenib

Description of PQI: Management of adverse effects related to Regorafenib treatment in metastatic colorectal cancer. Optimal dosing and follow up are essential to help patients benefit fully while taking this medication.

Background: Regorafenib is a multikinase inhibitor that has shown a median overall survival benefit (**6.4 months**, regorafenib + supportive care **versus 5.0 months,** placebo + supportive care; CORRECT Trial) in the third line setting. Keeping patients on therapy can be challenging due to the adverse effect profile of multikinase inhibitors.

Dose limiting side effects include (percentage refers to all grades):

- Skin and subcutaneous tissue adverse events, including palmar-plantar erythrodysesthesia (Hand and Foot syndrome) 72%[1]
- Mucositis 33%
- Diarrhea 43%
- Hypertension 30%
- Fatigue 64%
- Increased LFTs (AST-65%, ALT-45%, Bilirubin-45%)

The median time to first adverse event was 2 weeks with worst incidences occurring at 3 weeks. The worst severity of diarrhea occurred at 4 weeks (ASCO 2013, abstract 3637). Increases in LFTs usually occur within the first 8 weeks of therapy.

The **ReDOS trial** evaluated the dose escalation strategy in regorafenib patients and efficacy. A strategy with weekly dose escalation of regorafenib from 80 mg to 160 mg/day (Arm A) was found to be superior to a starting dose of 160 mg/day (Arm B). **A trend for improved OS was seen in the dose escalation arm.** The dose escalation strategy did not appear to compromise QOL. Patients started on 80mg for the first week with weekly dose escalations in the absence of significant drug-related toxicities. Median Overall Survival (OS) was improved in Arm A vs. Arm B (9.0 mos vs. 5.9 mos; p = 0.094). Median Progression Free Survival (PFS) was 2.5 mos for Arm A vs. 2.0 mos for Arm B (p=0.553).

ReDOS* trial presented at the ASCO GI Cancers Symposium 2018.
ReDOS poster from ASCO GI, Jan. 2018.
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A best practice for managing adverse events for patients receiving Regorafenib would be to establish a weekly follow up schedule for the first 8 weeks of therapy and also consider dose escalation. Pharmacist should exercise their clinical judgment after speaking with the patient and prescriber if the patient is a suitable candidate for the escalation strategy of Regorafenib. Document follow up schedule and dose escalation in EMR.

PQI process: Upon receipt of a new prescription for Regorafenib:

- If the typical starting dose of 160mg po QD is written, contact prescriber to discuss and potentially start patient on an escalation schedule such as the one described (**ReDOS trial strategy)**:
    - Initiate patient at 80mg for the first week of cycle #1
    - If no significant drug-related toxicities, escalate to 120mg for the second week of cycle #1, otherwise hold therapy at current dose
    - If no significant drug-related toxicities, escalate to 160mg for the third week of cycle #1, otherwise hold therapy at current dose
    - For following cycles, start therapy at current tolerated dose (no dose escalation)
- Coordinate and establish a weekly follow up call with the patient or caregiver for the first 8 weeks
- Monitor baseline LFTs
- Educate patients on side effects and report adverse effects to prescriber and recommend dose adjustments in 40 mg increments as tolerated[2]

Patient Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) sheet
- Provide patient starter kit
- Ensure patient knows dosing schedule (once daily for 3 weeks on and 1 week off)
- Ensure patient knows to take dose with a low-fat meal (<600 calories and 30% fat)
- Only open 1 bottle of Regorafenib at a time. **Medication expires 7 weeks after bottle is opened**
- Ensure patient or caregiver is able to take and record blood pressure at home daily
- Recommend Anti Diarrheals and Moisturizing cream i.e Urea 20%

Copay Assistance:

- Commercial patients can enroll in a $0 copay card assistance program (online enrollment- www.zerocopaysupport.com)

References:

1. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381(9863):303-312

2. NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines®) for colon cancer v.2.2018. © Page COL-D 9 of 10. National Comprehensive Cancer Network 2018. All rights reserved. Accessed May 10, 2018.

3. STIVARGA® (Regorafenib) [Prescribing Information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, April 2017.

4. Bekaii-Saab T, Ou FS, Ciombor KK, et al. Regorafenib dose optimization study (ReDOS): A phase II randomized study of lower starting dose regorafenib compared to standard dose regorafenib in patients with refractory metastatic colorectal cancer (mCRC). Journal of Clinical Oncology 2016 34:15_suppl, TPS3630-TPS3630