National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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Positive Quality Intervention: Neratinib Diarrhea Management

Description:
The purpose is to provide guidance on side effect prevention and management to minimize treatment interruptions. Diarrhea is a common side effect of Neratinib treatment occurring in 95% of patients in the ExteNET trial on the Neratinib arm.[1] The majority 93% of the patients experienced diarrhea in the first month of treatment so there is a great need for prevention and close patient monitoring during the first months of therapy.

Background:
Neratinib is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy. Neratinib is an irreversible tyrosine kinase inhibitor of human growth factor receptor 1, 2, and 4 (HER1, HER2, and HER4), as well as epidermal growth factor receptor (EGFR).

PQI Process:

Day 1- Initial Patient Counseling

- Make sure patient has instructions and supply of loperamide and consider colestipol (see figure 1 for dosing). Counsel patient on the importance of diarrhea prophylaxis and remind them that diarrhea occurs in 95% of the patients and grade 3 diarrhea was decreased from 30% in loperamide arm to 10% with the addition of colestipol according to the CONTROL Trial. While the CONTROL Trial reviewed 1 cycle, addressing diarrhea has been seen clinically covering 2 cycles. The average time to diarrhea is 8 days and prophylaxis diarrhea control should continue for a minimum of 2 cycles.
- Other possible side effects are nausea(43%), abdominal pain(36%), vomiting(26%) and stomatitis (14%).
- Neratinib should be taken with food and all six tablets(240mg) should be taken as one dose around the same time each day.
- Patient should be counseled on NOT taking neratinib along with PPIs or H2 antagonists and any other antacid should be given 3 hours prior to neratinib.
- Neratinib is a major substrate of CYP3A4 so avoid grapefruit juice and other medications that inhibits or increases CYP3A4.
- Advise patients to call office if diarrhea is uncontrolled with loperamide and colestipol. More than 4 loose stools per day over baseline.

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Patient follow-up - Consider following up 1 week after patient therapy initiation and then biweekly in following cycles as needed

- Assess diarrhea and ask how many loose stools the patient is having per day. Remind them to continue the loperamide and colestipol and report any uncontrollable diarrhea.
- Verify in your EMR that patient is scheduled for CMP to assess liver function this should be done prior to start and monthly for the first 3 months then every 3 months as clinically indicated.
- Assess if patient is having uncontrolled nausea or is developing stomatitis.
- Remind patient that they should not be taking any prescription or over the counter PPIs or H2 antagonists.

Adjustments for Toxicities: Consider discontinuing neratinib if toxicity does not recover to less than or equal to grade 1, for toxicities that result in a treatment delay of more than 3 weeks, or in patients unable to tolerate the 120 mg once daily dose

- **Recommended dose reduction for toxicity:**
  - First dose reduction 200mg once daily, second 160mg daily and third 120mg once daily.

- **Diarrhea: Grading**
  - **Grade 1:** Increase of <4 stools/day over baseline
  - **Grade 2:** Increase of 4 to 6 stools/day over baseline
  - **Grade 3:** Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living
  - **Grade 4:** Life-threatening consequences; urgent intervention necessary

- **Diarrhea: Interventions to discuss with medically integrated team**

  Grade 1, grade 2 (lasting <5 days), or grade 3 diarrhea (lasting <2 days):
    - Adding just antidiarrheal medication and diet
    - Maintain fluid intake of ~2 L.
    - When diarrhea has improved to ≤ grade 1 or baseline, initiate loperamide 4 mg with each subsequent neratinib dose.

Grade 2 diarrhea lasting ≥5 days or grade 3 diarrhea lasting longer than 2 days (despite optimal antidiarrheal management), or any grade diarrhea with complicating features (eg, dehydration, fever, hypotension, renal failure, or grade 3/4 neutropenia):

- Interrupt treatment. Modify diet; maintain fluid intake of ~2 L.
- If diarrhea improves to ≤ grade 1 in 1 week or less, resume neratinib at the same dose.
- If diarrhea improves to ≤ grade 1 in more than 1 week, resume neratinib at the next lower dose.
- When diarrhea has improved to ≤ grade 1 or baseline, initiate loperamide 4 mg with each subsequent neratinib dose.

Recurrent ≥ grade 2 diarrhea (occurring at 120 mg once daily dose):

- Permanently discontinue neratinib.

Grade 4 diarrhea:

- Permanently discontinue neratinib.

References:

1. NERLYNX [Package Insert]. Los Angeles, CA: Puma Biotechnology, Inc; 2017.
2. Hurvitz S, Chan A, Iannotti N, et al. Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2+ early-stage breast cancer: the CONTROL trial. Presented at: 40th Annual San Antonio Breast Cancer Symposium; December 5–9, 2017; San Antonio, TX. Poster P3-14-01.
3. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2016;17(3):367-377.

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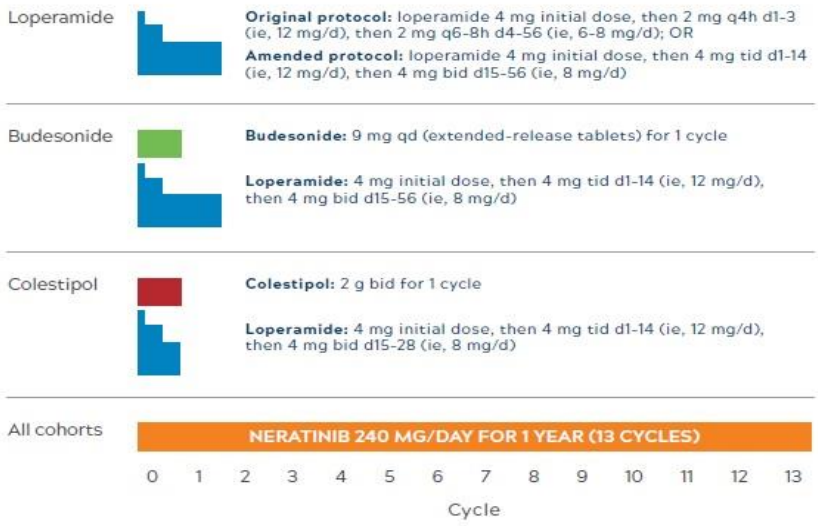
Supplemental Information

FIGURE 1: TREATMENT SCHEDULES BY COHORT



One cycle = 28 days
bid: twice daily; qd: once daily; tid: 3 times daily

Variable	CONTROL: Loperamide cohort (n = 137)	CONTROL: Loperamide + budesonide (n = 64)	CONTROL: Loperamide + colestipol (n = 120)	ExteNET: Loperamide prn (n = 1408)
Median cumulative duration, days				
Any grade	14.0	24.0	16.0	59.0
Grade ≥ 2	5.0	6.0	3.5	10.0
Grade ≥ 3*	3.0	2.0	3.0	5.0*
Median diarrhea episodes/patient				
Any grade	2	9	2.5	8
Grade ≥ 2	2	3	1	3
Grade ≥ 3*	1	1	1	2
Action taken, %				
Dose hold	15.3	18.8	9.2	33.9
Dose reduction	7.3	3.1	4.2	26.4
Discontinuation	20.4	10.9	1.7	16.8
Hospitalization	1.5	0	0	1.4

prn: pro re nata (as needed)
*One Grade 4 event reported in ExteNET.

- The occurrence and severity of diarrhea in the CONTROL study over the course of neratinib treatment was markedly reduced from that observed in the ExteNET study:
  - ExteNET showed a profile for diarrhea that was chronic and characterized by Grades 2 and 3 diarrhea with the greatest incidence in cycle 1 (month 1); and still observed in months 2-12
  - In the CONTROL study cohorts, the incidence of Grade 2-3 diarrhea was reduced during cycle 1 (month 1) and was also reduced in months 2-12
  - There appears to be some adaptation to the effects of neratinib, as higher-grade diarrhea occurs early during the course of treatment and is less common as treatment continues