Positive Quality Intervention: Neratinib Diarrhea Management

Description: Diarrhea is the main toxicity of neratinib (Nerlynx ®) treatment occurring in 95% of patients in the ExteNET trial on the Neratinib arm in which anti-diarrheal prophylaxis was not protocol specified. Various prevention and treatment strategies for diarrhea have been studied and will be discussed in this PQI.

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. The majority (93%) of patients experienced diarrhea in the first month of treatment in ExteNET. Median time to onset of any grade diarrhea is 2 days (8 days for Grade 3) and median cumulative duration of diarrhea was 59 days (5 days for Grade 3).

The Phase 2 CONTROL trial was designed to investigate various approaches to preventing and managing diarrhea in patients on neratinib, including various anti-diarrheal combinations, as well as a dose escalation arm. Mature data is available for budesonide and colestipol; interim data are available for dose escalation in Phase 2 CONTROL trial. All preventative strategies from the CONTROL trial reduced the incidence, duration, and severity of diarrhea, and also reduced neratinib discontinuation when compared to the pivotal ExteNET trial.

PQI Process:
Upon receipt of Neratinib prescription:
- Counsel patient on the importance of diarrhea prophylaxis and remind them that diarrhea occurs in 95% of the patients without prophylaxis protocol.
- The clinician should exercise his/her best professional judgment in making recommendations for interventions for individual patients.
- Begin prophylaxis with the first dose or neratinib and continue for 2 cycles depending on the regimen selected and the patient response.
- Ensure patient has instructions and supply of loperamide and consider colestipol or budesonide (see Supplemental Information for dosing).
- Consider dose escalation based on interim data from CONTROL trial (see Supplemental Information for dosing). Educate on PRN use of loperamide.
- Identify drug-drug interactions and side effect profiles of loperamide, colestipol, and budesonide when making clinical recommendations.
- Avoid concomitant use of PPIs. If H2-antagonists must be used, administer neratinib 2 hours before or 10 hours after. Other antacids (Tums, Maalox) should be separated by at least 3 hours.
- Verify in EMR that patient is scheduled for CMP to assess liver function.
Patient Centered Activities:
- Consider weekly assessment of diarrhea throughout the first 2 cycles
- Express importance of diarrhea prophylaxis and enable patients to obtain anti-diarrheal medications with manufacturer voucher
- Advise patients to call office if diarrhea is uncontrolled with anti-diarrheal regimen (more than 4 loose stools per day over baseline).
- Neratinib should be taken with food and all six tablets (240mg) should be taken as one dose around the same time with food each day.
- Maintain adequate oral hydration throughout treatment unless otherwise indicated by physician
- Consider monthly CMP for the first 3 months then every 3 months as clinically indicated.
- Counsel on other possible side effects are nausea (43%), abdominal pain (36%), vomiting (26%) and stomatitis (14%).
- Assess if patient is having uncontrolled nausea or is developing stomatitis or another AE.
- Clinicians should be aware of these new options for patients and the availability of a voucher for 3-months of anti-diarrheal medication at no charge from the manufacturer.

Dosage Adjustment for Diarrhea:
Grade 1 or 2 (<5 days) or Grade 3 (<2 days)
- Maximize use of antidiarrheal agents and assess diet and aggravating substances
- When diarrhea has improved to ≤ grade 1 or baseline, initiate loperamide 4 mg with each subsequent neratinib dose.

Grade 2 (>5 days) or Grade 3 (>2 days) or any grade with complicating features of 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 or more occurring at 120mg once daily dose, or, Grade 4 diarrhea:
- Permanently discontinue neratinib.

Important notice: National Community Oncology Dispensing Association, Inc. (NCODA), has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional.
References:

Supplemental Information

<table>
<thead>
<tr>
<th>Dosing Regimens from CONTROL study Loperamide:</th>
<th>4mg TID days 1-14, then 4mg BID days 15-56</th>
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<tbody>
<tr>
<td>Budesonide</td>
<td>9mg/day for 1 cycle</td>
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<tr>
<td></td>
<td>+ loperamide 4mg TID days 1-14, then 4mg BID days 15-56</td>
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<tr>
<td>Colestipol</td>
<td>2gm BID for 1 cycle + loperamide PRN or</td>
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<td></td>
<td>+ loperamide 4mg TID days 1-14, then 4mg BID days 15-28</td>
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<tr>
<td>Neratinib</td>
<td>120 mg/day on days 1–7, then 160 mg/day on days 8–14, then 240 mg/day through day 364, or</td>
</tr>
<tr>
<td></td>
<td>160 mg/day on days 1–14, then 200 mg/day on days 15–28, then 240 mg/day through day 364</td>
</tr>
</tbody>
</table>

Dose Escalation Regimen:
- 160mg (4 tablets) daily days 1-14
- 200mg (5 tablets) daily days 15-28
- 240mg (6 tablets) daily days 29+

Note: Loperamide was given PRN in this arm of the CONTROL study

Financial Assistance:
- 3-month voucher available for anti-diarrheal agents.
- Traditional financial assistance for high medication costs available through PumaPatientLynx. https://nerlynx.com/access-and-support

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Figure 1: CONTROL Trial: Strategies for Diarrhea Management

Median cumulative duration diarrhea per patient, days / year

Grade ≥2  Grade 3

10.0  5.0  5.0  6.0  4.0  3.5  10.0  3.0  3.0

ExteNET  Loperamide  Budesonide + loperamide  Colestipol + loperamide  Colestipol + loperamide PRN  Neratinib dose escalation

Figure 2: CONTROL Trial: Rates of Discontinuation due to Diarrhea

Incidence of Discontinuation due to Treatment-Emergent Diarrhea

Data for the neratinib dose-escalation cohort included here are not yet complete. As of April 2019, study treatment had been completed by 100% of patients in all cohorts except for the colestipol + loperamide prn (93.3%) and neratinib dose escalation + loperamide prn (6%) cohorts.


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