Effective Management and Prevention of Neratinib-Induced Diarrhea

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Abstract

Diarrhea is a common complication of many cancer treatments and a side effect well understood by most oncologists. It requires prompt and effective management to prevent sequelae, preserve dose intensity, and maintain patient quality of life. Neratinib (PB-272; Puma Biotechnology Inc, Los Angeles, CA, USA) is an irreversible pan-HER tyrosine kinase inhibitor in late-phase clinical development. Diarrhea, the most common toxicity associated with neratinib, is generally observed during the first cycle of treatment. Intensive loperamide prophylaxis (ie, 16 mg on day 1, tapering to 12 mg/day then 6-8 mg/day over the course of cycle 1) has been introduced in clinical trials of neratinib to better manage this toxicity. Safety data from these trials suggest that a prophylactic regimen reduces both the severity and duration of neratinib-associated diarrhea. Intensive loperamide prophylaxis should be used in all patients receiving neratinib for the first cycle of treatment.

Key words: Neratinib, diarrhea; prophylaxis, loperamide, clinical trials

Introduction

Neratinib (PB-272; Puma Biotechnology Inc, Los Angeles, CA, USA) is a potent small-molecule kinase inhibitor of human epidermal growth factor receptors HER1 (or EGFR1), HER2, and HER4.[1,2] It binds irreversibly to the intracellular ATP-binding pocket of the HER2 receptor and reduces receptor autophosphorylation.[2] *In vitro* studies show that neratinib blocks downstream signal transduction and cell cycle regulatory pathways in cancer cell lines, ultimately leading to decreased cell proliferation.[2] In animal studies, neratinib inhibits the growth of EGFR– and HER2–dependent tumor xenograft models when given orally on a once-daily schedule.[2]

Neratinib is currently in late-stage clinical development, with regulatory submission planned in 2016. It has been investigated extensively in the treatment of metastatic HER2–positive breast cancer both as a single agent[3-5] and in combination with chemotherapeutic and targeted agents.[6-11] Overall response rates in phase II studies ranged from 29% to 40% with neratinib monotherapy in women with metastatic HER2–positive breast cancer who had previously been treated with chemotherapy and trastuzumab.[3-5] Considerably higher response rates were observed when neratinib was combined with chemotherapeutic agents, for example, 63% with capecitabine[8] and 72% to 75% with neratinib plus paclitaxel.[6,10] Of note, neratinib showed clinical activity in women who had been previously treated with trastuzumab,[4,8] suggesting that it may be able to circumvent trastuzumab resistance.

Neratinib is also being investigated in early-stage HER2–positive breast cancer. In a phase III trial of neratinib (ExteNET), a 12-month course of treatment improved invasive disease-free survival after 2 years of follow-up compared with placebo in women with early-stage HER2–positive breast cancer after trastuzumab-containing adjuvant therapy (hazard ratio 0.67, 95% CI 0.50–0.91; 1-sided P = .0046).[12] Diarrhea was the most common adverse event with neratinib (grade 3, 40%; grade 4, <0.1%).[12] As previous efforts to improve outcomes with extended adjuvant therapy with trastuzumab have been unsuccessful,[13] neratinib is the first agent to significantly prolong disease-free survival in women with trastuzumab-treated early-stage breast cancer. Longer term follow-up and assessment of overall survival in the ExteNET trial is ongoing.

Neratinib is taken orally at a dosage of 240 mg once daily on a continuous schedule.[4] At this dosage, neratinib is generally well tolerated with a low incidence of grade 3/4 adverse events.[4] The most commonly reported adverse event and dose-limiting toxicity of neratinib is diarrhea,[3,4] a known class effect of EGFR-directed tyrosine kinase inhibitors.[14]

In this article, we will discuss the incidence, severity and patterns of occurrence of diarrhea with neratinib, and how this may be effectively managed with initiation of intensive loperamide prophylaxis at the beginning of treatment.

Cancer Treatment-Related Diarrhea

Grading

The standard tool most commonly used for grading the severity of diarrhea is the National Cancer Institute Common Toxicity Criteria (NCI-CTC) for Adverse Events.[15] According to version 4.0 of these criteria, grade 1 (mild) diarrhea is defined as an in-

TABLE 1. Chemotherapy Regimens and Targeted Agents Commonly Associated With Diarrhea. Data From Randomized Controlled Trials.

Agent or Regimen	Incidence of Diarrhea, %		Reference
	All grade	Grade 3/4	
Erlotinib	55	6	16
Gefitinib	34–47	<1–4	17,18
Afatinib	96	15	19
Lapatinib	48	7	20
Idelalisib	43	13	21
Lapatinib + capecitabine	65	14	22
Capecitabine + docetaxel	–	14	23
Cyclophosphamide, methotrexate + 5-fluorouracil	–	6	24
Pertuzumab, trastuzumab + docetaxel	67	8	25
Pertuzumab, trastuzumab, docetaxel + carboplatin	72	12	26
Panobinostat, bortezomib + dexamethasone	68	25	27
Irinotecan	76–82	16–36	28-30
5-Fluorouracil/leucovorin			
Bolus (Mayo Clinic)	58–64	12–21	31-34
Bolus (Roswell Park)	79	29–30	32,35
Infusional (LV5FU2)	44–48	4–7	34,36-38
FOLFOX4	46–61	5–12	37-41
FOLFIRI	59–63	10–14	41-46
FOLFOXIRI	78	20	46
Capecitabine	46–48	11–12	31,33
XELOX	60–65	19–20	39,47
Bevacizumab + FOLFIRI	57	11–14	44,48
Cetuximab + FOLFIRI	63	11–16	45,48
Cetuximab + irinotecan	81	21–28	29,49
Panitumumab + FOLFIRI	–	14	43

FOLFIRI indicates infused 5-fluorouracil, leucovorin, plus irinotecan; FOLFOX, infused 5-fluorouracil, leucovorin, plus oxaliplatin; FOLFOXIRI, infused 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; XELOX, capecitabine plus oxaliplatin.

crease of <4 stools per day from baseline (or mild increase in ostomy output), with asymptomatic or mild symptoms such that intervention is not indicated.[15] Grade 2 (moderate) diarrhea is defined as an increase of four to six stools per day from baseline (or moderate increase in ostomy output), requiring minimal, local, or non-invasive interventions only.[15] Grade 3 (severe or medically significant) diarrhea is defined as an increase of ≥7 stools per day from baseline (or severe increase in ostomy output), incontinence, hospitalization (or prolongation of hospitalization) limiting self-care activities of daily living.[15] Grade 4 events are deemed to be life-threatening requiring urgent intervention.[15] In clinical practice, patient symptom diaries are also generally used as an additional assessment tool in conjunction with the NCI-CTC criteria.

Occurrence

Diarrhea is a common side effect of many cancer treatments, including chemotherapeutic agents, molecularly targeted agents and pelvic radiotherapy. EGFR-directed tyrosine kinase inhibitors are associated with high frequencies of clinically important diarrhea, and depending on the agent, up to 95% of patients may experience some grade of diarrhea, although the risk of grade 3/4 events tends to be lower (<15%) (**Table 1**). Diarrhea is also common with several multi-agent HER2–directed regimens used in the treatment of HER2–positive breast cancer (**Table 1**). Further, it is recognized that regimens used for the treatment of colorectal cancer, particularly those involving fluoropyrimidines and irinotecan, carry a high risk of diarrhea.[50] Data from randomized trials suggest that up to 80% of patients treated with regimens involving these agents may experience diarrhea, and 20% will commonly experience grade 3 or 4 diarrhea (**Table 1**).

Management

Diarrhea caused by cancer treatments requires early intervention to prevent complications such as dehydration, electrolyte imbalances, and renal insufficiency.[51] If left unmanaged, persistent diarrhea can require additional resources beyond oral antidiarrheal agents (fluid replacement, octreotide, antibiotics, unplanned clinic visits, hospitalization) and can be costly to manage.[52,53] Severe diarrhea can also lead to changes in treatment, including dose reductions and treatment discontinuation.[52-54] These alterations may have a negative effect on tumor control, although the consequences of diarrhea-driven treatment modifications and discontinuations on clinical outcomes have never been formally investigated.

Effective management should involve a continuous process of assessment, reassessment, and appropriate dietetic and pharmacological interventions, with an increase in aggressive stepwise management as needed. There are several sets of guidelines for the management of cancer treatment-related diarrhea,[50,51,55-59] although there is little consensus between them on the details of care. Treatment is often empirical and the guidelines have

served to highlight that there are few clinically relevant studies on which to base decisions relating to the management of cancer treatment-related diarrhea.[5]

Pharmacological treatment of cancer treatment-related diarrhea is based primarily on the empirical use of opioids. Loperamide, a synthetic opiate, is the standard first-line treatment for chemotherapy-induced diarrhea.[50,59] It acts as an agonist on opioid receptors in the gastrointestinal tract to decrease gut motility.[51] Systemic absorption of loperamide and systemic adverse events are minimal, although high-dose therapy can lead to paralytic ileus.[55] Alternative opioids recommended for cancer treatment-related diarrhea include deodorized tincture of opium[50,59] and diphenoxylate plus atropine (Lomotil®).[59] Octreotide is the other main pharmacologic intervention for cancer treatment-related diarrhea. It is generally reserved for use in complicated cases or as a second-line treatment for persistent diarrhea after loperamide.[50] Octreotide is a somatostatin analogue that decreases hormone secretion to prolong intestinal transit time, promote intestinal absorption of electrolytes, and decrease mesenteric blood flow.[51] It is well tolerated, with the most common adverse events being mild abdominal pain and injection site pain.[60]

Other than the use of atropine for early cholinergic diarrhea associated with irinotecan infusion,[61] prophylactic anti-diarrheal therapy is not standard for any cancer treatment. Several small studies have investigated the utility of different prophylactic anti-diarrheal regimens to reduce the frequency and severity of cancer treatment-related diarrhea. Activated charcoal[62] and oral alkalinization[63] may be beneficial for irinotecan-associated diarrhea, and probiotics may have a role in preventing 5-fluorouracil (5-FU)-related diarrhea.[64] However, studies of prophylactic octreotide[65-67] and an intestinal adsorbent[68] did not show benefit.

Many studies have investigated potential risk factors for the development of cancer treatment-related diarrhea (ie, genotype, clinical characteristics), although prospective studies are lacking and no predictors are used in clinical practice. Readers are referred to Andreyev et al[55] for a more detailed discussion of this subject.

Occurrence of Diarrhea with Neratinib

Studies with No or Suboptimal Antidiarrheal Prophylaxis

Diarrhea management in initial trials of neratinib involved treatment with antidiarrheal agents and/or dose modifications only after diarrheal symptoms became apparent. A few studies included antidiarrheal prophylaxis, but the doses of loperamide used were proven to be suboptimal (ie, 2 or 4 mg/day).[7,69,70] For example, in the Translational Breast Cancer Research Consortium 022 phase II study, the incidence of grade 3 diarrhea was 33% before the introduction of prophylaxis compared with 21% with low-dose loperamide prophylaxis (2 mg/day).[69]

From the studies with no or suboptimal prophylaxis, it was evident that most diarrhea events with neratinib occurred in the first month of treatment. For example, in the ExteNET trial, the overall incidence of grade 3 or higher diarrhea was 40%; however, 73% of these patients experienced grade 3 events during the first month of treatment. After the third month of treatment, grade 3 diarrhea was relatively infrequent with approximately 6% of patients on treatment or fewer experiencing grade 3 diarrhea after month 3. The rate of grade 2 diarrhea also declined from about 30% in the first month to 18% to 19% in months 2 and 3, and to 12% in month 12 (data on file, Puma Biotechnology Inc.).

Practical Application

- Diarrhea is a common side effect of many cancer treatments and can lead to severe complications and treatment modifications if left unmanaged. Diarrhea is the most common adverse event of neratinib, a novel irreversible pan-HER tyrosine kinase inhibitor.
- Most higher-grade diarrhea with neratinib occurs during the first cycle of treatment.
- For effective management, neratinib should be used in conjunction with an intensive regimen of loperamide prophylaxis for the first cycle of treatment.

In studies with no or suboptimal prophylaxis, treatment-emergent diarrhea with neratinib was generally of mild-to-moderate severity; grade 1/2 events occurred in 56% to 67% of patients (**Table 2**).[4,12,61] The incidence of grade 3 diarrhea ranged from 30% to 53% (**Table 2**),[4,9,12,70] with an incidence of 40% in the largest study performed to date (ExteNET).[12] Where details of grade 4 events were available, these events were rare (0% to 3% of patients).[3,4,6,7,9,10,12,69] The median duration of all grade events was 7 to 14 days per episode as reported in two studies (**Table 2**).

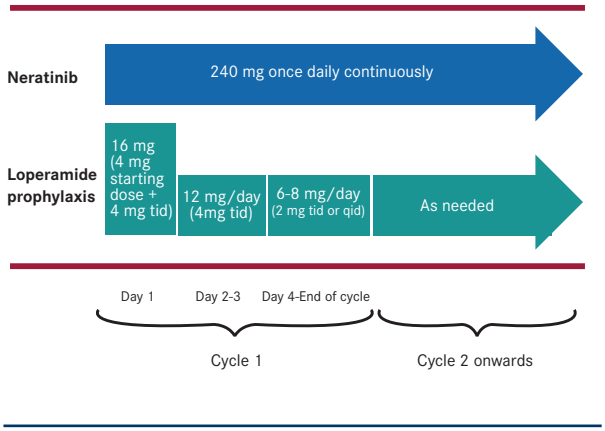
Diarrhea resolved in most patients either spontaneously or with standard management involving antidiarrheal medications and/or dose modifications.[5] Neratinib dose reductions because of diarrhea were documented in 10% to 15% of patients.[5,8,10] Most patients continued treatment despite the occurrence of diarrhea, and treatment discontinuation as a result of diarrhea was uncommon (0% to 14% of patients).[3-6,8,10,12,71]

Studies with Intensive Loperamide Prophylaxis

The mainstay of management for neratinib-associated diarrhea is intensive prophylaxis with loperamide. An intensive prophylactic regimen was first instigated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) FB-8 study after the investigators noted a high occurrence of diarrhea in the first week of neratinib therapy despite early treatment with loperamide.[9] Prophylaxis was initiated with the first dose of neratinib and given for the first cycle of treatment. Although the patient numbers in the NSABP FB-8 study were small, the introduction of intensive loperamide prophylaxis reduced the occurrence of grade 3 diarrhea from 53% (8 of 15 patients) before its introduction to 0% (0 of 6 patients).[9]

Based on the early success of this regimen, intensive antidiarrheal prophylaxis with loperamide for the first cycle of treatment has been introduced as a mandatory measure in new and on-

FIGURE 1. Intensive Loperamide Prophylactic Regimen for Use With Neratinib



qid, 4-times daily; tid, 3-times daily.

going trials of neratinib. The precise loperamide regimen used in these studies has evolved over the past 2 years to improve patient compliance. However, the initial dose of loperamide has remained constant (ie, 4 mg with the first dose of neratinib), and all regimens have tapered to a lower dose of loperamide over the course of the first cycle. The recommended loperamide prophylactic regimen for use with neratinib is shown in **Figure 1**.

Safety data from trials that included intensive loperamide prophylaxis show a marked reduction in the incidence of grade 3 diarrhea to 0% to 17%, even though many of the patients who experienced grade 3 diarrhea did not receive the full prophylactic regimen due to compliance issues (**Table 2**).[9,70,72] This compares with rates of 30% to 53% in studies with no or suboptimal prophylaxis (**Table 2**). The median duration of all-grade treatment-emergent diarrheal events was also reduced from 7 to 14 days to 2 days with loperamide prophylaxis (**Table 2**).

A detailed management algorithm for treatment-emergent diarrhea during neratinib therapy is shown in **Figure 2**. Any

FIGURE 2. Management Plan for Neratinib-Related Diarrhea

Treatment-emerged diarrhea

Dietetic

DIETETIC MEASURES
- Stop all lactose-containing products.
- Drink 8 to 10 large glasses of clear liquids per day.
- Eat frequent small meals.
- Recommend low-fat diet enriched with bananas, rice, apple sauce and toast, ie, BRAT diet.

FLUID INTAKE
- Fluid intake (~2L) should be maintained.

Pharmacological treatment

PHARMACOLOGIC INTERVENTIONS

FIRST-LINE THERAPY - LOPERAMIDE
- If receiving prophylaxis, increase loperamide dose to a maximum of 16 mg/day.
- If new-onset diarrhea, take loperamide 4 mg with first bout of diarrhea followed by 2 mg every 4 hours or after every unformed stool (maximum 16 mg/day). Continue until diarrhea-free for 12 hours.
- With recovery to ≤ grade 1, take loperamide 4 mg with each subsequent neratinib administration.

SECOND-LINE THERAPY

Grade 1
- If persistent diarrhea on loperamide, add diphenoxylate hydrochloride plus atropine sulfate (Lomotil®) 2.5 mg every 6 to 8 hours.

Grade 2
- If persistent diarrhea on loperamide, add octreotide (short-acting) 150 µg subcutaneously tid, or after initial dose of short-acting octreotide, if well tolerated, a single dose of octreotide LAR 20 mg intramuscularly.

Grade 3/4
- After intensive loperamide therapy, titrate loperamide to keep diarrhea controlled (<4 stools/day).
- Octreotide (100 to 150 µg subcutaneously bid or 25 to 50 µg/hour intravenously if dehydration is severe, with dose escalation up to 500 µg subcutaneously tid).
- Intravenous fluids as appropriate.
- Consider prophylactic antibiotics, especially if diarrhea is persistent beyond 24 hours or if there is fever or grade 3/4 neutropenia.
- Stool cultures to exclude infectious causes.

Dose modifications

Uncomplicated cases*

NERATINIB
- Continue at full dose (neratinib 240 mg)

Persistent or complicated cases**

NERATINIB
- First occurrence: hold neratinib until ≤ grade 1.

If recovery occurs:
- ≤1 week, resume same dose neratinib.
- 1 to 4 weeks, reduce neratinib dose.

Second occurrence: reduce neratinib dose.
Subsequent occurrences: reduce neratinib dose.

Neratinib dose reduction levels: 160 and 120 mg.

* Grade 1 diarrhea, grade 2 diarrhea lasting <5 days, or grade 3 diarrhea lasting <2 days.
** Grade 2 diarrhea lasting >5 days or grade 3 diarrhea lasting >2 days despite optimal treatment or associated with fever, dehydration, or grade 3-4 neutropenia, or any grade 4 diarrhea.
bid indicates twice daily; tid, 3-times daily.

TABLE 2. Occurrence of Diarrhea With Neratinib in Selected Studies With No or Suboptimal Prophylaxis and Studies That Included Intensive Loperamide Prophylaxis.

Study	No or Suboptimal Loperamide Prophylaxis				Loperamide Prophylaxis[a]				
	NSABP FB-8	10-005	3144A1-201	ExteNET	NSABP FB-8	10-005	PUMA-NER-4201		PUMA-NER 5201
Population	HER2+ MBC	HER2+ MBC	HER2+ MBC	HER2+ EBC	HER2+ MBC	HER2+ MBC	HER2-mutated NSCLC		HER family mutated solid tumors
Study treatment	Neratinib + trastuzumab + paclitaxel	Neratinib + temsirolimus	Neratinib	Neratinib	Neratinib + trastuzumab + paclitaxel	Neratinib + temsirolimus	Neratinib + temsirolimus	Neratinib	Neratinib
Total patients, n	15	37[b]	66[f]	1408	6	41	14	13	81
Grade 1/2	–[c]	21 (57)	44 (67)[f]	781 (56)	5 (83)	24 (59)	12 (86)	9 (69)	37 (46)
Grade 3	8 (53)	12 (32)	20 (30)[d,f]	562 (40)[d]	0	7 (17)	2 (14)	1 (8)	10 (12)
Patients with grade 3 diarrhea who were noncompliant[e] with loperamide, n (%)	–	–	–	–	0	4/7 (57)	1/2 (50)	1/1 (100)	–
Median duration of all-grade treatment-emergent diarrhea per episode, days.	–	14	7[f]	–	–	2	2	2	2
Trial registration	NCT01423123	NCT01111825	NCT00300781	NCT00878709	NCT01423123	NCT01111825	NCT01827267		NCT01953926
References	9	70; data on file, Puma Biotechnology Inc	4; data on file, Puma Biotechnology Inc	12; data on file, Puma Biotechnology Inc	9; data on file, Puma Biotechnology Inc	70; data on file, Puma Biotechnology Inc	72; data on file, Puma Biotechnology Inc		Data on file, Puma Biotechnology Inc

[a]Loperamide 4 mg administered with the first dose of neratinib, followed by 2 mg every 4 hours for 3 days, then 2 mg every 6 to 8 hours for the remainder of cycle 1.
[b]Patients received low-dose loperamide prophylaxis (4 mg/day).
[c]Grade 1 and 2 diarrhea rate was 52% (11 out of 21 patients); however, patient numbers by cohort were not provided.
[d]Includes 1 grade 4 event.
[e]Defined as less than 10 mg/day on day 1, 8 mg/day on days 2 or 3, or 6 mg/day until the end of cycle 1.
[f]Patients with prior trastuzumab therapy.
EBC indicates early-stage breast cancer; MBC, metastatic breast cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project; NSCLC, non-small cell lung cancer

new-onset diarrhea may be managed with the maximum dose of loperamide (ie, 16 mg/day), with the addition of diphenoxylate plus atropine (Lomotil®) or octreotide according to severity. Dietetic changes, such as the BRAT diet (ie, low-fat diet enriched with bananas, rice, applesauce, and toast), increased fluid intake, stopping all lactose-containing products, and frequent small meals, should also be encouraged. Treatment interruptions or dose reductions are recommended only if patients have significant persistent diarrhea and are unresponsive to the above-mentioned interventions.

Future Research With Neratinib

A comprehensive clinical development program of neratinib is currently ongoing (**Table 3**). In a recently reported phase III trial (ExteNET), treatment with neratinib demonstrated a statistically significant improvement in invasive disease-free survival com-

TABLE 3. Ongoing Clinical Trials With Neratinib.

	Protocol (Name)	Registration Identifier	Phase	Cancer	Setting	Treatment
HER2-overexpressing or -amplified breast cancer	3144A2-3004-WW (ExteNET)	NCT00878709	III	Early-stage breast cancer	Adjuvant (post-trastuzumab)	Neratinib *vs* placebo
	PUMA-NER-6201	NCT02400476	II	Early-stage breast cancer	Adjuvant (post-trastuzumab)	Neratinib
	NSABP FB-7	NCT01008150	II	Early-stage breast cancer	Neoadjuvant	Neratinib + paclitaxel *vs* trastuzumab + paclitaxel *vs* neratinib + trastuzumab + paclitaxel
	PUMA-NER-1301 (NALA)	NCT01808573	III	Metastatic breast cancer	Third-line	Neratinib + capecitabine *vs* lapatinib + capecitabine
	10-005	NCT01111825	I/II	Metastatic breast cancer	Trastuzumab-refractory	Neratinib + temsirolimus
	TBCRC 022	NCT01494662	II	Metastatic breast cancer	CNS metastases	Neratinib ± capecitabine
	NSABP FB-10	NCT02236000	I/II	Metastatic breast cancer	Second-line	Neratinib + trastuzumab emtansine
ERBB-mutated cancers	201209135	NCT01670877	II	*ERBB2*-mutated metastatic breast cancer	First and later lines	Neratinib ± fulvestrant
	PUMA-NER-4201	NCT01827267	II	*ERBB2*-mutated advanced/metastatic NSCLC	First and later lines	Neratinib ± temsirolimus
	PUMA-NER-5201 (BASKET)	NCT01953926	II	Solid tumors (*ERBB*-mutated or EGFR amplified)	Incurable	Neratinib
Other cancers	NSABP FC-7	NCT01960023	I/II	Wild-type *KRAS, NRAS, BRAF, PIK3CA* metastatic colorectal cancer	Second and later lines	Neratinib + cetuximab

CNS indicates central nervous system; EGFR, epithelial growth factor receptor; NSABP, National Surgical Adjuvant Breast and Bowel Project; NSCLC, non-small cell lung cancer; TBCRC, Translational Breast Cancer Research Consortium.

pared with placebo in patients with early-stage HER2–positive breast cancer who had previously received adjuvant trastuzumab. However, because no antidiarrheal prophylaxis was given in ExteNET, the rate of grade 3 (or higher) diarrhea was high (40%).[12] To better understand the ability of high-dose loperamide prophylaxis to reduce neratinib-related diarrhea, a phase II study (PUMA-NER 6201) has been initiated to formally investigate the effectiveness of this loperamide prophylaxis regimen. Similar to ExteNET, the study is enrolling women with early-stage HER2–positive breast cancer following trastuzumab-based adjuvant therapy. All patients are receiving neratinib 240 mg/day plus intensive loperamide prophylaxis (ie, 4 mg with the first dose of neratinib, 4 mg 3-times daily for 2 weeks, then 4 mg twice daily). The primary outcome of the study is the incidence and severity of diarrhea, and secondary outcomes include the incidence and severity of diarrhea by loperamide exposure.

In addition, there are several other phase II and III trials of neratinib with loperamide prophylaxis in patients with early-stage and metastatic HER2–positive breast cancer (**Table 3**). NALA (PUMA-NER-1301) is a randomized phase III trial that is comparing neratinib plus capecitabine with lapatinib plus capecitabine as third-line therapy in patients with HER2–positive metastatic breast cancer. The study was prompted by the findings of an earlier phase II study that reported notable activity with neratinib plus capecitabine.[8] NALA will enroll approximately 600 patients from centers in Europe, Asia-Pacific, and North

and South America. The coprimary study endpoints are progression-free survival and overall survival. Further phase II studies are testing neratinib alone or as part of a combination in tumors with HER2 or HER3 mutations, or EGFR-amplified tumors.

The precise molecular mechanism of neratinib-induced diarrhea is unknown, but is postulated to be due to EGFR inhibition and resultant secretory diarrhea.[55] Preclinical studies are ongoing to better characterize the histopathology, clinical symptoms, and blood biochemistry of neratinib-induced diarrhea, and to understand the on-target effects of neratinib on the gastrointestinal system and the specific mechanisms of the neratinib-related diarrhea.

Conclusions

Diarrhea is a recognized adverse event of many cancer treatments and a side effect well understood by most oncologists. Once diarrhea occurs, it should be managed promptly and aggressively to prevent an escalation in severity and patient morbidity, and to maintain full-dose therapy. Diarrhea is a class effect of EGFR-directed tyrosine kinase inhibitors, and the most common toxicity of neratinib, a novel irreversible pan-HER tyrosine kinase inhibitor. For patients receiving neratinib, preventive management with intensive loperamide prophylaxis is required to reduce the severity and duration of diarrhea. Loperamide prophylaxis should be started with the first dose of treatment and continued until the end of the first cycle, regardless of the presence or absence of diarrhea. Any treatment-emergent diarrhea should be managed according to standard guidelines.

Initial trials with neratinib were all performed without the support of effective antidiarrheal prophylaxis. Intensive loperamide prophylaxis has been implemented and refined in ongoing and new trials of the drug. Preliminary safety data from these trials suggest that active management with intensive loperamide prophylaxis reduces the incidence, severity, and duration of neratinib-associated diarrhea. The frequency of grade 3 diarrhea when neratinib is given with intensive loperamide prophylaxis (0% to 17%) is similar to rates observed with other EGFR-directed tyrosine kinase inhibitors (1% to 14%), and considerably lower than rates observed with many chemotherapy regimens used in routine oncology practice (**Table 1**).

Intensive loperamide prophylaxis provides an effective means of reducing the incidence, severity and duration of neratinib-associated diarrhea. It should be given for the first cycle of treatment in all patients receiving neratinib. Current diarrhea prophylaxis recommendations are 4 mg with the first dose of neratinib, then 4 mg 3 times on day 1 (for a total of 16 mg on day 1), 4 mg 3-times daily (for a total of 12 mg/day) on days 2 and 3, reducing to 2 mg 3- or 4-times daily (for a total of 6-8 mg/day) for the remainder of the first cycle. Nonpharmacologic interventions, including dietetic changes and increased fluid intake, are recommended for new-onset uncomplicated diarrhea.

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