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ORIGINAL ARTICLE

NOLAN: a randomized, phase 2 study to estimate the effect of prophylactic naproxen or loratadine vs no prophylactic treatment on bone pain in patients with early-stage breast cancer receiving chemotherapy and pegfilgrastim

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Abstract

Purpose Mild-to-moderate bone pain is a commonly reported adverse event (AE) associated with pegfilgrastim. We evaluated the effect of prophylactic naproxen or loratadine vs no prophylactic treatment on pegfilgrastim-associated bone pain.
Methods In this open-label study (NCT01712009), women ≥ 18 years of age with newly diagnosed stage I–III breast cancer and an ECOG performance status ≤ 2 who were planning ≥ 4 cycles of adjuvant or neoadjuvant chemotherapy with pegfilgrastim support starting in cycle 1 were randomized 1:1:1 to receive naproxen, loratadine, or no treatment to prevent pegfilgrastim-associated bone

pain. The primary endpoint was all-grade bone pain in cycle 1 from AE reporting. Secondary endpoints included bone pain in cycles 2–4 and across all cycles from AE reporting and patient-reported bone pain by cycle and across all cycles.
Results Six hundred patients were enrolled. Most patients (83.0%) were white, and mean (SD) age was 54.2 (11.1) years. The percentage of patients with all-grade bone pain in cycle 1 from AE reporting in the naproxen, loratadine, and no prophylaxis groups was 40.3, 42.5, and 46.6%, respectively; differences between the treatment groups were not statistically significant. Maximum, mean, and area under the curve for patient-reported bone pain were consistently lower in the naproxen and loratadine groups than in the no prophylaxis group; some of these differences were significant. Loratadine was associated with fewer treatment-related AEs and discontinuations than naproxen.
Conclusions Given its tolerability, its ease of administration, and its potential benefit, treatment with loratadine should be considered to help prevent bone pain in patients receiving chemotherapy and pegfilgrastim.
Clinical trial registration ClinicalTrials.gov; NCT01712009

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Background

Febrile neutropenia, the combination of low neutrophil count and fever, is a life-threatening consequence of myelosuppressive chemotherapy that may necessitate hospitalization and administration of intravenous antibiotics [1–3]. Primary

prophylaxis with pegfilgrastim reduces the risk of febrile neutropenia in patients with nonmyeloid malignancies receiving chemotherapy [4–7].

Mild-to-moderate bone pain is a commonly reported adverse event (AE) associated with pegfilgrastim [8–11], though the reported incidence of bone pain varies considerably among studies [5, 10–15]. Differences in the incidence of bone pain could be due to differences among patient populations, chemotherapy regimens (e.g., inclusion of taxanes), stage of malignancy and bone involvement, previous therapies, concurrent medication (e.g., use of opioids), and diligence regarding collection of data on AEs.

Bone pain is of considerable concern to patients, because the pain may be severe. Patients may refuse pegfilgrastim, and physicians may stop using pegfilgrastim to avoid bone pain; this may increase the chance of infection, hospitalization, and mortality [3, 16]. Utilization of less intensive regimens as a strategy to reduce the risk of febrile neutropenia may negatively impact treatment outcomes, particularly in curative settings such as early-stage breast cancer [17–19].

Several studies have suggested that naproxen (a nonsteroidal anti-inflammatory drug) and loratadine (an antihistamine) may each be effective in preventing pegfilgrastim-associated bone pain [20–25]. In this randomized, open-label, multicenter study (NOLAN: Naproxen Or Loratadine And Neulasta; NCT01712009), we evaluated the effect of prophylactic naproxen, prophylactic loratadine, or no prophylactic treatment on bone pain in patients with breast cancer receiving chemotherapy and pegfilgrastim.

Methods

Patients

Eligible patients were women ≥ 18 years of age with newly diagnosed stage I–III breast cancer not previously treated with chemotherapy and an Eastern Cooperative Oncology Group performance status ≤ 2, who were planning to receive ≥ 4 cycles of adjuvant or neoadjuvant chemotherapy with pegfilgrastim support starting in cycle 1 and continuing throughout each of the first 4 chemotherapy cycles. Patients were excluded if they were planning to receive weekly chemotherapy, had ongoing chronic pain or other painful conditions requiring treatment (including immediate postoperative treatment), were chronically using oral steroidal and/or nonsteroidal anti-inflammatory drugs or oral antihistamines, had received prior chemotherapy for cancer within 5 years of the current breast cancer diagnosis, or had previously received granulocyte colony-stimulating factor (G-CSF; filgrastim, pegfilgrastim, or other). Patients were also excluded if they had a history of clinically significant gastrointestinal (GI)

bleeding, a history of GI ulcers, or active GI bleeding within 6 months prior to randomization. A full listing of inclusion and exclusion criteria is presented in the Supplemental material. This study was conducted in accordance with United States Food and Drug Administration and International Conference on Harmonization Good Clinical Practice regulations/guidelines. All patients provided written informed consent.

Study design

Each eligible patient received adjuvant or neoadjuvant chemotherapy, with pegfilgrastim prophylaxis beginning in the first cycle and continuing through each of the first four chemotherapy cycles. Patients could receive chemotherapy regimens with > 4 cycles; however, data were collected only for the first 4 cycles. Pegfilgrastim (6 mg; Neulasta®, Amgen Inc., Thousand Oaks, CA) was administered as a subcutaneous injection between 24 and 72 h after chemotherapy. Choice of chemotherapy regimen (agent, dose, and schedule) was at the discretion of the treating physician. The investigational medicinal products assessed in the study were naproxen and loratadine; pegfilgrastim and chemotherapy were considered background therapy.

After screening, eligible patients were stratified by age group (< 65 vs ≥ 65 years) and planned chemotherapy type (taxane vs nontaxane). Patients were then randomized in a 1:1:1 ratio within each stratum to receive prophylactic naproxen, prophylactic loratadine, or no prophylactic treatment. Prophylactic naproxen or loratadine was administered orally for 5 days in each of the first 4 chemotherapy cycles, beginning on the day patients received pegfilgrastim. Naproxen (500 mg) was administered twice a day, in the morning and in the evening. Loratadine (10 mg) was administered once a day in the morning. A study schema is shown in Fig. 1.

Data on bone pain were captured by asking patients about any AEs they had experienced since their last clinic visit. On day 1 of cycles 2, 3, and 4 and at the safety follow-up visit that occurred 30–37 days after the last dose of study treatment in cycle 4, healthcare providers asked patients if they had experienced any AEs since their last visit. If patients reported bone pain, the healthcare provider asked the patients to rate the severity of the pain at its worst. Bone pain reported to healthcare providers outside of these scheduled visits was also captured. AEs were coded using the Medical Dictionary for Regulatory Activities, version 18.0. Severity of AEs was graded using Common Terminology Criteria for Adverse Events, version 3.0.

Data on bone pain were also captured using patient surveys. In each of the first 4 chemotherapy cycles, patients were asked to complete a brief bone pain survey once per day for 5 days, beginning the day they received pegfilgrastim. The
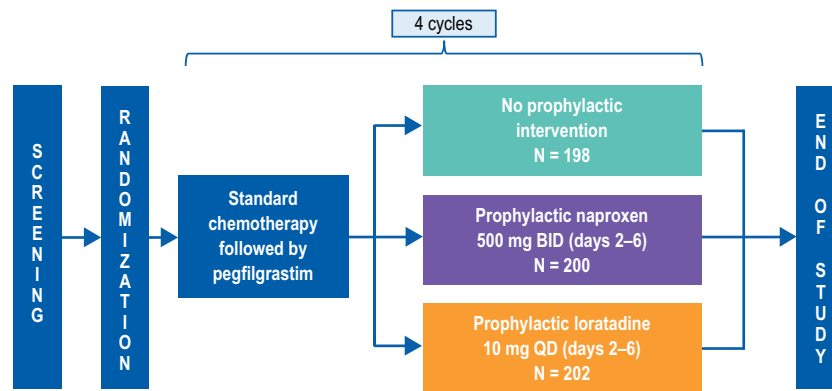
Fig. 1 Study schema. Following screening and randomization, patients received chemotherapy followed 24–72 h later by pegfilgrastim. Patients initiated treatment with naproxen or loratadine on the same day they received pegfilgrastim. Data on bone pain AEs were collected on day 1 of cycles 2, 3, and 4 and at the safety follow-up visit. Patients completed bone pain surveys and bone pain medication logs once per day for 5 days, beginning the day they received pegfilgrastim in cycles 1–4. *BID* twice a day, *QD* once a day

bone pain survey captured information on the severity of pain (on a scale of 0–10) and the location(s) of pain. The bone pain survey filled out in each cycle by patients in the naproxen arm is shown in Supplemental Fig. 1; similar surveys were filled out by patients in the loratadine and no prophylaxis arms. Patients placed the completed bone pain surveys in sealed envelopes and returned them to the study site at their next clinic visit. The bone pain surveys were retained in their sealed envelopes until patients had completed the study and all AEs reported by the patients had been recorded. Healthcare providers did not supplement AE reports with information gathered from patient surveys.

Patients were asked to record detailed information on any medications taken to alleviate bone pain in a bone pain medication log. This log included fields for the name of the medication taken, the dose of each tablet, and the number of tablets taken per day. Logs were reviewed with healthcare providers at the next clinic visit.

Throughout the study, investigators could prescribe any medications or treatments deemed necessary to provide adequate supportive care, except investigational agents or prophylactic medications for pain relief other than those to which patients were randomized as part of the study. Premedication related to the administration of chemotherapy and use of antiemetics were allowed per usual clinical practice.

Endpoints

The primary endpoint of the study was bone pain (all grades combined) in cycle 1, captured as part of AE reporting. The secondary endpoints were bone pain (all grades combined) by cycle in cycles 2–4 and across all cycles (cycles 1–4) from AE reporting, severe (grade 3 or 4) bone pain by cycle and across all cycles from AE reporting, patient-reported bone pain by cycle and across all cycles, maximum patient-reported bone pain by cycle and across all cycles, and area under the curve (AUC) for patient-reported bone pain (a measure of total pain) by cycle and across all cycles. The safety endpoints were incidence and severity of AEs.

Statistical analyses

This was an estimation study, and it was not powered to demonstrate a statistically significant difference between treatment groups for any endpoints. Differences between treatment groups were not tested formally, and P values are considered nominal. The clinical hypothesis was that an absolute reduction of 10% in all-grade bone pain in the treatment groups compared to the control group could suggest a clinical benefit. The sample size of 600 patients was selected based on data from randomized controlled studies [20, 21].

The following standard summary statistics were calculated: frequency, percentage, and 95% confidence intervals (CIs) for categorical variables; and number, mean, median, minimum, maximum, 95% CI, and standard deviation (SD) for continuous variables. Analysis of the primary and secondary endpoints was based on the full analysis set, which included all patients who received prophylaxis with pegfilgrastim. Analysis was repeated within subgroups based on the stratification factors used in randomization (age < 65 vs ≥ 65 years, taxane vs nontaxane chemotherapy). Since the study did not test any formal statistical hypotheses, no controls for multiple comparisons were employed.

Analysis of AEs was based on the safety analysis set, which included all patients in the full analysis set, according to the prophylactic medication actually received rather than according to randomization. Patient incidence of AEs was summarized for all AEs, treatment-emergent AEs, serious AEs, treatment-related AEs, and AEs leading to withdrawal of naproxen or loratadine.

Missing patient-reported bone pain survey data were imputed using multiple imputation [26]; imputation methodology

was applied using SAS® version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient enrollment and disposition

The study was conducted at 83 centers in the USA between November 1, 2012 (first patient enrolled), and March 18, 2015 (last patient completed the study). Overall, 600 patients were enrolled and randomized: 200 to the naproxen group, 202 to the loratadine group, and 198 to the no prophylaxis group. A total of 391 patients (97.3%) received at least 1 dose of naproxen or loratadine: 193 received naproxen and 198 received loratadine. A total of 587 patients (97.8%) received at least 1 dose of pegfilgrastim (constituting the full analysis set). A CONSORT diagram is shown in Supplemental Fig. 2.

Baseline demographics, disease characteristics, and chemotherapy

All 587 patients in the full analysis set were women. Of these, 83.0% ($n = 487$) were white, 14.1% ($n = 83$) were black, and 1.2% ($n = 7$) were Asian. Mean (SD) age was 54.2 (11.1) years; 80.9% ($n = 475$) were < 65 years and 19.1% ($n = 112$) were ≥ 65 years of age. Patient demographics and disease characteristics were largely balanced between the treatment groups. Baseline demographics, disease characteristics, and stratification factors used in randomization are shown in Table 1. Chemotherapy regimens received by patients are shown in Supplemental Table 1. The use of prednisone or dexamethasone, two drugs commonly used in antiemetic regimens, was reported in > 90% of patients (no prophylaxis, 98.4% [$n = 188$]; naproxen, 94.9% [$n = 186$]; loratadine, 92.5% [$n = 185$]).

Bone pain from AE reporting

All-grade bone pain from AE reporting

In cycle 1, all-grade bone pain was reported by 46.6% ($n = 89$) of patients in the no prophylaxis group, 40.3% ($n = 79$) in the naproxen group, and 42.5% ($n = 85$) in the loratadine group. The differences (95% CIs) between the percentages of patients who reported all-grade bone pain in the naproxen group and the no prophylaxis group and between the loratadine group and the no prophylaxis group in cycle 1 were − 6.3% (− 16.7, 4.1%) and − 4.1% (− 14.5, 6.3%), respectively. None of the differences between the treatment groups in cycle 1 were nominally significant at the 5% level. Differences between the treatment groups in cycles 2–4 were not meaningful; all-

grade bone pain was most frequently reported in cycle 1. All-grade bone pain from AE reporting is shown in Table 2.

Across all cycles, all-grade bone pain was reported by 63.4% ($n = 121$) of patients in the no prophylaxis group, 59.2% ($n = 116$) in the naproxen group, and 61.0% ($n = 122$) in the loratadine group. The differences (95% CIs) between the percentages of patients who reported all-grade bone pain in the naproxen group and the no prophylaxis group and between the loratadine group and the no prophylaxis group across all cycles were − 4.2% (− 14.4, 6.0%) and − 2.4% (− 12.5, 7.8%), respectively (Table 2).

Analysis of bone pain from AE reporting in subgroups based on stratification factors at randomization (age < 65 vs ≥ 65 years, taxane vs nontaxane chemotherapy) did not show any meaningful differences between the treatment groups in the number of patients who reported bone pain.

Severe (grade 3 or 4) bone pain from AE reporting

No grade 4 bone pain was reported in this study. In cycle 1, severe (grade 3) bone pain was reported by 4.7% ($n = 9$) of patients in the no prophylaxis group, 3.1% ($n = 6$) in the naproxen group, and 4.5% ($n = 9$) in the loratadine group. Across all cycles, severe bone pain was reported by 5.8% ($n = 11$) of patients in the no prophylaxis group, 4.1% ($n = 8$) in the naproxen group, and 4.5% ($n = 9$) in the loratadine group. Severe bone pain from AE reporting is shown in Supplemental Table 2. None of the differences between the treatment groups were nominally significant at the 5% level, and none of the analyses of severe bone pain in patient subgroups showed any meaningful differences between the treatment groups.

Bone pain from patient surveys

Patient-reported maximum bone pain

Missing values for patient-reported bone pain scores were imputed. The amount of missing bone pain survey data across all cycles was 8.4% in the no prophylaxis arm, 7.2% in the naproxen arm, 3.4% in the loratadine arm, and 6.3% total.

Estimated differences in maximum patient-reported bone pain indicated a nominally significant treatment benefit for naproxen in cycle 4 ($P = 0.032$) and for loratadine in cycle 1 ($P = 0.006$), cycle 4 ($P = 0.032$), and across all cycles ($P = 0.041$) (Table 3).

Among patients < 65 years of age, a treatment benefit for naproxen was observed in cycle 1 ($P = 0.015$) and cycle 4 ($P = 0.032$). A treatment benefit for loratadine was observed in cycle 1 ($P = 0.002$), cycle 4 ($P = 0.020$), and across all cycles ($P = 0.015$) (Supplemental Table 3). Among patients ≥ 65 years of age, no treatment benefit for either naproxen or loratadine was observed (Supplemental Table 4).

Table 1 Baseline demographics, disease characteristics, and stratification factors used in randomization (full analysis set)

	No prophylaxis (N = 191)	Naproxen 500 mg BID (N = 196)	Loratadine 10 mg QD (N = 200)	Total (N = 587)
Race, n (%)				
White	148 (77.5)	166 (84.7)	173 (86.5)	487 (83.0)
Black (or African American)	33 (17.3)	27 (13.8)	23 (11.5)	83 (14.1)
Asian	3 (1.6)	3 (1.5)	1 (0.5)	7 (1.2)
Other[a]	7 (3.7)	0 (0.0)	3 (1.5)	10 (1.7)
Age, years				
Mean (SD)	54.8 (10.7)	53.2 (11.7)	54.6 (10.9)	54.2 (11.1)
Min, max	29, 82	24, 82	18, 81	18, 82
Age group[b], n (%)				
Stratified to < 65 was < 65 years	156 (81.7)	158 (80.6)	162 (81.0)[c]	476 (81.1)[c]
Stratified to ≥ 65 was ≥ 65 years	35 (18.3)	38 (19.4)	38 (19.0)	111 (18.9)
Calculated BSA[d], m^2				
Mean (SD)	1.899 (0.235)	1.875 (0.240)	1.881 (0.217)	1.885 (0.231)
Min, max	1.38, 2.62	1.36, 2.77	1.33, 2.64	1.33, 2.77
Disease stage, n (%)				
I	58 (30.4)	41 (20.9)	51 (25.5)	150 (25.6)
II	94 (49.2)	96 (49.0)	104 (52.0)	294 (50.1)
III	39 (20.4)	59 (30.1)	45 (22.5)	143 (24.4)
Histology, n (%)				
Ductal carcinoma	158 (82.7)	167 (85.2)	169 (84.5)	494 (84.2)
Lobular carcinoma	18 (9.4)	18 (9.2)	19 (9.5)	55 (9.4)
Other[e]	15 (7.9)	11 (5.6)	12 (6.0)	38 (6.5)
Nodal status, n (%)				
0	87 (45.5)	85 (43.4)	93 (46.5)	265 (45.1)
1–3	81 (42.4)	82 (41.8)	89 (44.5)	252 (42.9)
≥ 4	19 (9.9)	28 (14.3)	14 (7.0)	61 (10.4)
Missing	4 (2.1)	1 (0.5)	4 (2.0)	9 (1.5)
Chemotherapy regimen[b], n (%)				
Stratified to taxane received taxane	88 (46.1)	94 (48.0)	92 (46.0)	274 (46.7)
Stratified to taxane received nontaxane	19 (9.9)	17 (8.7)	21 (10.5)	57 (9.7)
Stratified to nontaxane received nontaxane	83 (43.5)	84 (42.9)	85 (42.5)	252 (42.9)
Stratified to nontaxane received taxane	1 (0.5)	1 (0.5)	2 (1.0)	4 (0.7)

The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

BID twice a day, BSA body surface area, QD once a day, SD standard deviation

[a] Other includes American Indian or Alaska Native, multiple races, native Hawaiian or other Pacific Islander, and other

[b] Stratification factor used in randomization

[c] One patient stratified to < 65 was actually ≥ 65 years of age

[d] Calculated BSA = square root of (height in cm × weight in kg)/3600

[e] Other includes inflammatory breast cancer, colloid carcinoma, metaplastic carcinoma, and other

Among patients in the taxane-based chemotherapy stratum, no treatment benefit for naproxen was observed, but a treatment benefit for loratadine was observed in cycle 1 (P = 0.040) (Supplemental Table 5). Among patients in the nontaxane-based chemotherapy stratum, no treatment benefit for naproxen was observed, but a treatment benefit for loratadine was observed in cycle 1 (P = 0.039), cycle 2 (P = 0.019), cycle 4 (P = 0.021), and across all cycles (P = 0.035) (Supplemental Table 6).

Patient-reported mean bone pain

Estimated differences in mean patient-reported bone pain indicated a nominally significant treatment benefit for naproxen

Table 2 All-grade bone pain from AE reporting (full analysis set)

All-grade bone pain	No prophylaxis (N = 191)	Naproxen 500 mg BID (N = 196)	Loratadine 10 mg QD (N = 200)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1, n (%)[a]	191 (100.0)	196 (100.0)	200 (100.0)			
Patients who reported bone pain	89	79	85			
Percentage	46.6	40.3	42.5	− 6.3	− 4.1	2.2
95% CI for percentage[b]	(39.4, 53.9)	(33.4, 47.5)	(35.6, 49.7)	(− 16.7, 4.1)	(− 14.5, 6.3)	(− 8.0, 12.4)
Cycle 2, n (%)[a]	178 (93.2)	180 (91.8)	193 (96.5)			
Patients who reported bone pain	61	62	67			
Percentage	34.3	34.4	34.7	0.2	0.4	0.3
95% CI for percentage[b]	(27.3, 41.7)	(27.5, 41.9)	(28.0, 41.9)	(− 10.2, 10.6)	(− 9.8, 10.7)	(− 9.9, 10.5)
Cycle 3, n (%)[a]	165 (86.4)	176 (89.8)	188 (94.0)			
Patients who reported bone pain	56	60	68			
Percentage	33.9	34.1	36.2	0.2	2.2	2.1
95% CI for percentage[b]	(26.8, 41.7)	(27.1, 41.6)	(29.3, 43.5)	(− 10.5, 10.8)	(− 8.3, 12.8)	(− 8.3, 12.4)
Cycle 4, n (%)[a]	162 (84.8)	169 (86.2)	179 (89.5)			
Patients who reported bone pain	66	68	68			
Percentage	40.7	40.2	38.0	− 0.5	− 2.8	− 2.2
95% CI for percentage[b]	(33.1, 48.7)	(32.8, 48.0)	(30.9, 45.5)	(− 11.7, 10.7)	(− 13.7, 8.2)	(− 13.1, 8.6)
Across all cycles, n (%)[a]	191 (100.0)	196 (100.0)	200 (100.0)			
Patients who reported bone pain	121	116	122			
Percentage	63.4	59.2	61.0	− 4.2	− 2.4	1.8
95% CI for percentage[c]	(56.1, 70.2)	(52.0, 66.1)	(53.9, 67.8)	(− 14.4, 6.0)	(− 12.5, 7.8)	(− 8.3, 12.0)

The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

AE adverse event, *BID* twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day

[a] For individual cycles, *n* and percentage are based on the number of patients who entered the cycle. For across all cycles, *n* and percentage are based on the number of patients who started chemotherapy

[b] CIs for percentages are calculated using binomial distribution. CIs for the difference between percentages are calculated using Fleiss's method with continuity correction

in cycle 4 ($P = 0.029$) and for loratadine in cycle 1 ($P = 0.016$) and across all cycles ($P = 0.044$) (Supplemental Table 7).

Among patients < 65 years of age, a treatment benefit for naproxen was observed in cycle 1 ($P = 0.028$), cycle 4 ($P = 0.020$), and across all cycles ($P = 0.029$). A treatment benefit for loratadine was observed in cycle 1 ($P = 0.006$) and across all cycles ($P = 0.016$) (Supplemental Table 8). Among patients ≥ 65 years of age, no treatment benefit for either naproxen or loratadine was observed (Supplemental Table 9).

Among patients in the taxane-based chemotherapy stratum, no treatment benefit for either naproxen or loratadine was observed (Supplemental Table 10). Among patients in the nontaxane-based chemotherapy stratum, no treatment benefit for naproxen was observed, but a treatment benefit for loratadine was observed in cycle 1 ($P = 0.024$), cycle 2 ($P = 0.007$), cycle 4 ($P = 0.023$), and across all cycles ($P = 0.014$) (Supplemental Table 11).

Table 3 Patient-reported maximum bone pain (scale 0–10) by cycle and across all cycles (full analysis set)

Maximum patient-reported bone pain[a]	No prophylaxis (N = 191)	Naproxen 500 mg BID (N = 196)	Loratadine 10 mg QD (N = 200)	Difference (naproxen minus no prophylaxis)	Difference (loratadine minus no prophylaxis)	Difference (loratadine minus naproxen)
Cycle 1						
n[b]	191	196	200			
Mean (SE)	3.9 (0.2)	3.3 (0.2)	3.0 (0.2)	−0.6 (0.3)	−0.9 (0.3)	−0.2 (0.3)
95% CI[c]	(3.4, 4.4)	(2.8, 3.7)	(2.6, 3.4)	(−1.3, 0.0)	(−1.5, −0.3)	(−0.9, 0.4)
P value[c]				0.059	**0.006**	0.427
Cycle 2						
n[b]	178	180	193			
Mean (SE)	3.0 (0.2)	2.4 (0.2)	2.6 (0.2)	−0.6 (0.3)	−0.4 (0.3)	0.1 (0.3)
95% CI[c]	(2.5, 3.4)	(2.0, 2.8)	(2.2, 2.9)	(−1.2, 0.0)	(−1.0, 0.2)	(−0.5, 0.7)
P value[c]				0.071	0.148	0.673
Cycle 3						
n[b]	165	176	188			
Mean (SE)	2.7 (0.2)	2.2 (0.2)	2.5 (0.2)	−0.5 (0.3)	−0.2 (0.3)	0.3 (0.3)
95% CI[c]	(2.3, 3.2)	(1.8, 2.6)	(2.1, 2.9)	(−1.1, 0.1)	(−0.8, 0.4)	(−0.3, 0.9)
P value[c]				0.092	0.487	0.287
Cycle 4						
n[b]	162	169	179			
Mean (SE)	2.8 (0.2)	2.1 (0.2)	2.1 (0.2)	−0.7 (0.3)	−0.6 (0.3)	0.0 (0.3)
95% CI[c]	(2.3, 3.3)	(1.7, 2.5)	(1.8, 2.5)	(−1.3, −0.1)	(−1.2, −0.1)	(−0.5, 0.6)
P value[c]				**0.032**	**0.032**	0.889
Across all cycles						
n[b]	191	196	200			
Mean (SE)	4.7 (0.2)	4.2 (0.2)	4.1 (0.2)	−0.5 (0.3)	−0.7 (0.3)	−0.2 (0.3)
95% CI[c]	(4.3, 5.2)	(3.8, 4.7)	(3.6, 4.5)	(−1.1, 0.2)	(−1.3, −0.0)	(−0.8, 0.5)
P value[c]				0.147	**0.041**	0.569

Note: All missing values of patient-reported bone pain within any cycle were imputed. P values < 0.05 are shown in bold. The full analysis set includes all patients who received primary prophylaxis with pegfilgrastim

BID twice a day, *CI* confidence interval, *N* number of patients in the analysis set, *QD* once a day, *SE* standard error

[a] Maximum patient-reported bone pain is the maximum value of each patient's bone pain values across survey days 1–5 within each cycle. Across all cycles, the maximum is the maximum value of each patient's reported bone pain values across all survey days 1–5 across all cycles

[b] For individual cycles, *n* is based on the number of patients who entered the cycle. For across all cycles, *n* is based on the number of patients who started chemotherapy

[c] The 95% CI and P value are calculated using an analysis of variance (ANOVA) model, with differences calculated using pairwise least-squares mean differences

AUC for patient-reported bone pain

Estimated differences in AUC for patient-reported bone pain over the first 5 days in each cycle (beginning the day patients received pegfilgrastim) indicated a nominally significant treatment benefit for naproxen in cycle 4 ($P = 0.027$) and for loratadine in cycle 1 ($P = 0.012$) and across all cycles ($P = 0.033$) (Fig. 2 and Supplemental Table 12). AUC for patient-reported bone pain was highest for all treatment groups in cycle 1.

Among patients < 65 years of age, a treatment benefit for naproxen was observed in cycle 1 ($P = 0.028$), cycle 4

($P = 0.020$), and across all cycles ($P = 0.028$). A treatment benefit for loratadine was also observed in cycle 1 ($P = 0.005$), cycle 4 ($P = 0.049$), and across all cycles ($P = 0.010$) (Supplemental Table 13). Among patients ≥ 65 years of age, no treatment benefit for either naproxen or loratadine was observed (Supplemental Table 14).

Among patients in the taxane-based chemotherapy stratum, no treatment benefit for either naproxen or loratadine was observed (Supplemental Table 15). Among patients in the nontaxane-based chemotherapy stratum, no treatment benefit for naproxen was observed, but a treatment benefit for loratadine was observed in cycle 1 ($P = 0.016$), cycle 2

Table 4 Patients reporting treatment-related AEs, serious treatment-related AEs, and treatment-related AEs leading to discontinuation of naproxen or loratadine (safety analysis set)

	Naproxen 500 mg BID (N = 193) n (%)	Loratadine 10 mg QD (N = 198) n (%)
Patients reporting treatment-related AEs[a]	30 (15.5)	7 (3.5)
Worst grade of ≥ 2	11 (5.7)	3 (1.5)
Worst grade of ≥ 3	2 (1.0)	0 (0.0)
Worst grade of ≥ 4	0 (0.0)	0 (0.0)
Serious AEs	1 (0.5)	0 (0.0)
Life-threatening AEs	0 (0.0)	0 (0.0)
Fatal AEs	0 (0.0)	0 (0.0)
Patients reporting treatment-related AEs by system organ class and preferred term (≥ 1% of patients in any group), n (%)		
Gastrointestinal disorders	21 (10.9)	1 (0.5)
Nausea	5 (2.6)	1 (0.5)
Abdominal pain	3 (1.6)	0 (0.0)
Constipation	3 (1.6)	1 (0.5)
Dyspepsia	3 (1.6)	0 (0.0)
Diarrhea	2 (1.0)	1 (0.5)
Gastroesophageal reflux disease	2 (1.0)	0 (0.0)
Vomiting	2 (1.0)	0 (0.0)
General disorders and administration site conditions	5 (2.6)	5 (2.5)
Fatigue	3 (1.6)	4 (2.0)
Nervous system disorders	3 (1.6)	2 (1.0)
Headache	3 (1.6)	1 (0.5)
Skin and subcutaneous tissue disorders	3 (1.6)	1 (0.5)
Blood and lymphatic system disorders	2 (1.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (1.0)	1 (0.5)
Patients reporting treatment-related AEs leading to discontinuation of naproxen or loratadine	9 (4.7)	0 (0.0)
Patients reporting AEs leading to discontinuation of naproxen or loratadine by system organ class and preferred term (≥ 1% of patients in any treatment group)		
Gastrointestinal disorders	7 (3.6)	0 (0.0)
Abdominal pain	3 (1.6)	0 (0.0)

The safety analysis set includes all patients who received primary prophylaxis with pegfilgrastim; allocation to treatment groups is based on prophylactic medication actually received

AE adverse event, *BID* twice a day, *QD* once a day

[a] Treatment-related AEs are AEs associated with naproxen and loratadine (not chemotherapy or pegfilgrastim)

(P = 0.004), cycle 4 (P = 0.016), and across all cycles (P = 0.009) (Supplemental Table 16).

Additional bone pain medications from medication logs

Patients recorded information on medications taken reactively to alleviate bone pain in bone pain medication logs. In cycle 1, 63.9% of patients in the no prophylaxis group, 33.2% in the naproxen group, and 42.5% in the loratadine group took additional bone pain medications. Across all cycles, 73.8% of patients in the no prophylaxis group, 44.9% in the naproxen group, and 57.5% in the loratadine group took additional bone pain medications. The percentage of patients who took additional bone pain medications declined from cycle 1 to cycle 2 to cycles 3 and 4. Data on patients who took additional bone pain medications are shown in Supplemental Fig. 3 and Supplemental Table 17. The additional analgesics taken by the most patients were paracetamol, ibuprofen, and vicodin; the additional NSAIDs taken by the most patients were ibuprofen and naproxen sodium; the additional antihistamine taken by the most patients was loratadine. Additional analgesics, antihistamines, and NSAIDs from medication logs are listed in Supplemental Table 18.

Fig. 2 AUC for patient-reported bone pain (scale 0–10) by cycle and across all cycles. Patient-reported bone pain AUC was calculated using the trapezoidal rule with bone pain scores from day 1 through 5 of each cycle. Numerical values for the means and the 95% CIs are noted. Mean AUC across cycles was the average of AUCs across the cycles. *AUC* area under the curve, *CI* confidence interval, *L* loratadine, *N* naproxen, *NP* no prophylaxis
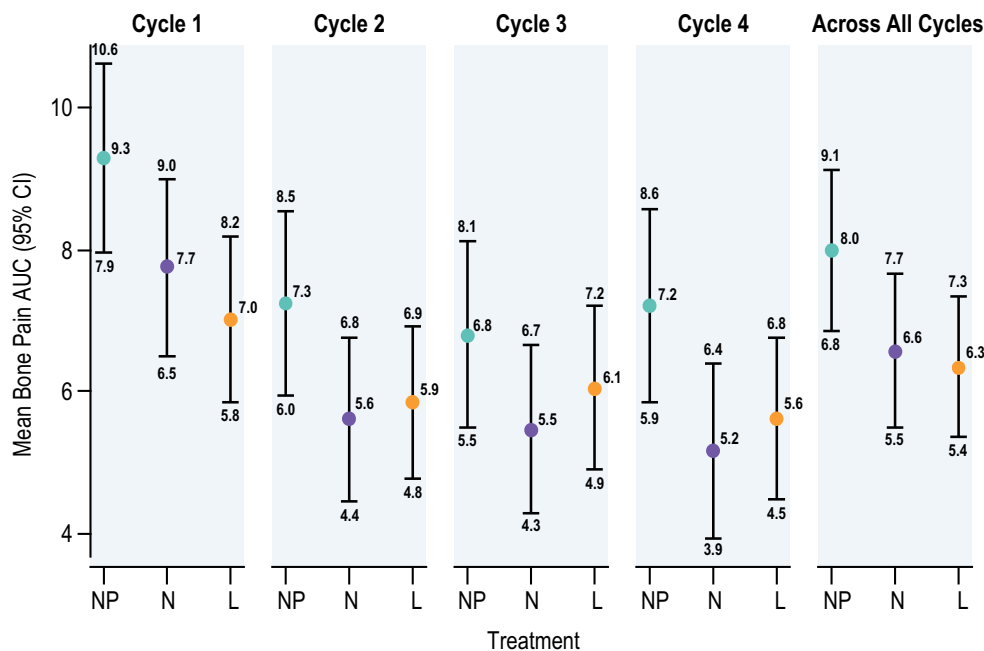
Patient-reported bone pain by survey day and range in cycle 1

The frequency distribution of patient-reported bone pain on each survey day in cycle 1 was calculated. The percentage of patients across groups who reported moderate (score 4–6) or severe bone pain (score 7–10) was 10.6% ($n = 62$) on survey day 1 (the day of pegfilgrastim administration), 22.8% ($n = 134$) on day 2, 30.7% ($n = 180$) on day 3, 27.8% ($n = 163$) on day 4, and 22.0% ($n = 129$) on day 5. The percentage of patients across groups who reported no bone pain (score 0) or mild bone pain (score 1–3) was 84.8% ($n = 498$) on day 1, 71.7% ($n = 421$) on day 2, 64.2% ($n = 377$) on day 3, 66.6% ($n = 391$) on day 4, and 71.7% ($n = 421$) on day 5. Bone pain (score 1–10) across groups was lowest on day 1 and highest on day 3. These data are presented in Supplemental Fig. 4 and Supplemental Table 19.

Safety

Thirty patients (15.5%) in the naproxen group and 7 patients (3.5%) in the loratadine group reported treatment-related AEs (Table 4). One patient in the naproxen group had two serious treatment-related AEs: GI hemorrhage and peptic ulcer. Treatment-related GI disorders were reported by 21 patients (10.9%) in the naproxen group and 1 patient (0.5%) in the loratadine group. GI disorders were the most common reason for discontinuation of naproxen. There were no reports of treatment-related neutropenia or febrile neutropenia in this study, and there were no treatment-related life-threatening or fatal AEs. Cases of treatment-emergent neutropenia and febrile neutropenia were generally balanced across the treatment groups. Treatment-emergent AEs that occurred in $\geq 5\%$ of patients in any treatment group are shown in Supplemental Table 20.

Discussion

Bone pain is a commonly reported AE associated with pegfilgrastim use [5, 9–15], and some patients experience such severe pain that they opt to discontinue pegfilgrastim [22]. This may increase the incidence of infection [17, 27, 28] and may negatively affect outcomes, as dose delays, dose reductions, and reduced chemotherapy dose intensity may increase the cancer recurrence rate and decrease overall survival [1, 18, 29, 30].

We evaluated the effect of prophylactic naproxen, prophylactic loratadine, or no prophylactic treatment on pegfilgrastim-associated bone pain. The primary objective was to estimate the differences between the treatment groups in the percentage of patients who reported all-grade bone pain in cycle 1 as part of AE reporting. The differences between the treatment groups that we observed were not nominally significant at the 5% level. A reduction of 10% in bone pain in the naproxen or loratadine groups compared to the no prophylaxis group was used as a benchmark for clinically meaningful benefit. However, the differences between the groups that we observed were less than 10%. Differences in the percentage of patients who reported all-grade bone pain in cycles 2–4 and across all cycles and the percentage of patients who reported severe (grade 3 or 4) bone pain by cycle and across

all cycles were not meaningful. While these results have implications for the efficacy of naproxen and loratadine, they also have implications for AE reporting as an instrument for data collection. Asking patients once per chemotherapy cycle (i.e., every 2, 3, or 4 weeks) whether they have experienced any AEs since their last visit may not be an adequately sensitive way of collecting information on subjective measures such as pain [31, 32].

Patient-reported outcomes are potentially a much better way of collecting data on pain than AE reporting [33–35], and they are gradually gaining acceptance as instruments for reporting symptoms [36–38]. Patient surveys revealed that maximum bone pain, mean bone pain, and AUC for bone pain were lower in the naproxen and loratadine groups than in the no prophylaxis group in some cycles. Some of these differences were nominally significant at the 5% level. Most importantly, patient-reported bone pain was consistently lower in the naproxen and loratadine groups than in the no prophylaxis group by every measure.

A large amount of information on bone pain severity was collected in this study. Across treatment groups, severe bone pain from AE reporting was more common in cycle 1 than in subsequent cycles. Maximum patient-reported bone pain was highest in cycle 1 and consistently lower in cycles 2, 3, and 4. In cycle 1, the percentage of patients across treatment groups who reported moderate (score 4–6) or severe bone pain (score 7–10) increased from day 1 (the day of pegfilgrastim administration) to day 2, peaked on day 3, and then declined on day 4 and then again on day 5. This information may be of interest to patients and healthcare providers as they prepare for treatment or guide the treatment of others.

Among patient subgroups based on stratification factors at randomization (age < 65 vs ≥ 65 years, taxane vs nontaxane chemotherapy), there was consistent evidence for a treatment benefit for naproxen and loratadine among patients < 65 years of age and those stratified to nontaxane-based chemotherapy. Little treatment benefit was observed among patients ≥ 65 years of age and those stratified to taxane-based chemotherapy. As this was an estimation study, and controls for multiple comparisons were not employed, results of the subgroup analyses should be interpreted with caution.

The number of patients with treatment-related AEs was higher in the naproxen group than in the loratadine group; the difference between the arms in treatment-related AEs was greatest for gastrointestinal disorders. The number of patients with ≥ grade 3 treatment-related AEs and serious treatment-related AEs was higher in the naproxen arm than in the loratadine arm, and more patients discontinued naproxen. Loratadine may therefore be a better choice than naproxen for patients receiving chemotherapy. Naproxen may also be avoided in patients receiving myelosuppressive

chemotherapy due to its inhibition of platelet aggregation and its antipyretic effects.

This study lends support to previous studies that have shown a treatment benefit for naproxen and loratadine in the prophylaxis of pegfilgrastim-associated bone pain. Kirshner et al. showed that naproxen reduced the incidence and severity of pegfilgrastim-induced bone pain [22], and showed in pilot studies that loratadine may also reduce bone pain [21, 23]. Two case reports reported similar findings on loratadine and bone pain [24, 39]. Pawloski et al. reported that loratadine was the most common medication used to treat bone pain, but did not assess the effectiveness of this intervention [40]. A study by Moukharskaya et al. reported that loratadine did not significantly reduce pain among patients who reported significant back or leg bone pain following an initial dose of pegfilgrastim [41]. The authors proposed a number of possible explanations for this outcome: only patients who experienced significant pain in cycle 1 entered the treatment phase of the trial, patients were permitted to use analgesics for bone or other pain, and patients filled out the FACT-BP questionnaire only twice over two cycles of chemotherapy [41]. A recent study by Gavioli et al. reported that double histamine blockade (using a combination of famotidine and loratadine) was effective in alleviating bone pain secondary to G-CSF use [42].

The present study was a prospective, randomized, three-arm trial conducted in 600 patients. As such, it is the largest study conducted to date to assess prophylactic agents for the prevention of pegfilgrastim-induced bone pain. Despite these strengths, the study had several limitations. This was an estimation study with no formal hypothesis testing, and P values should therefore be considered nominal. There was no statistical adjustment for multiple comparisons, and the number of patients in some subgroups was small. Treatment with naproxen and loratadine was open-label, and patients in the no prophylaxis group did not receive placebo. Patients were free to take medications reactively for bone pain during the study, and more patients in the no prophylaxis group than in the naproxen or loratadine groups took medications for bone pain; this may have reduced the observed treatment benefit for naproxen and loratadine. Patients in this study received a variety of chemotherapy regimens, and different levels of bone pain may be associated with these regimens. Premedication related to the administration of chemotherapy and use of antiemetics were allowed per usual clinical practice. Use of prednisone and dexamethasone, two drugs commonly used in antiemetic regimens, was balanced across the treatment arms, but both premedication and antiemetics may have reduced the impact of the interventions in this study. All patients in the study were women and had early-stage breast cancer, so these results may not translate to men or other tumor types and stages. Subgroup analyses were based on stratification factors at randomization, and treatment did not always align with stratification.

Conclusions

This study has implications for both patient quality of life and cancer treatment. Prophylactic use of daily naproxen or loratadine could potentially reduce pegfilgrastim-associated bone pain and help maintain adherence with planned chemotherapy. This may improve treatment outcomes. Healthcare providers should carefully weigh risks and benefits when deciding on a course of treatment for each patient, and they should be cognizant of the potential dangers of polypharmacy. Nevertheless, given its tolerability, its ease of administration, and the consistent reductions in patient-reported bone pain observed in this study, treatment with 5 days of once daily loratadine in each chemotherapy cycle should be considered for patients receiving chemotherapy and pegfilgrastim.

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