Prevention of Pegfilgrastim-Induced Bone Pain: A Phase III Double-Blind Placebo-Controlled Randomized Clinical Trial of the University of Rochester Cancer Center Clinical Community Oncology Program Research Base

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See accompanying editorial on page 1907 and article on page 1980; listen to the podcast by Dr Von Roenn at www.jco.org/podcasts

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ABSTRACT

Purpose

Pegfilgrastim-induced bone pain is a significant clinical problem that may result in discontinuation of pegfilgrastim and lead to less effective chemotherapy dosing. Interventions for pegfilgrastim-induced bone pain are needed.

Patients and Methods

The University of Rochester Cancer Center Clinical Community Oncology Program Research Base randomly assigned 510 patients at 17 sites to receive either naproxen (500 mg two times per day) or placebo on the day of pegfilgrastim administration, continuing for 5 to 8 days after pegfilgrastim. Patients recorded pain severity (using a scale of 0 to 10) and duration in daily diaries. The primary outcome measure was the area under the curve (AUC) for pain for days 1 through 5. Secondary outcome measures included the identification of risk factors for the development of pain and response to naproxen.

Results

Patients' mean age was 55.6 years and 86% were female. Sixty-eight percent of patients had breast cancer and 10% had lung cancer. Pain reached its peak at 3 days for both groups. The mean AUC for pain was 7.71 for the placebo group and 6.04 for the naproxen group ($P = .037$). Naproxen reduced maximum pain from 3.40 to 2.59 ($P = .005$). Naproxen also reduced overall pain incidence from 71.3% to 61.1% ($P = .020$) and duration from 2.40 to 1.92 days ($P = .009$). The reduction in severe pain (> 5 on a scale of 1 to 10) from 27.0% to 19.2% was also significant ($P = .048$). Risk factors could not be identified to predict incidence, severity, or ability to prevent pegfilgrastim-induced bone pain.

Conclusion

Our phase III randomized placebo-controlled clinical trial demonstrated that naproxen at a dose of 500 mg twice per day is effective in reducing the incidence and severity of pegfilgrastim-induced bone pain.

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INTRODUCTION

The development of pegfilgrastim represents a significant clinical advance and has helped oncologists administer full-dose myelosuppressive chemotherapy on schedule.¹⁻⁴ Pegfilgrastim has also enabled the development of dose-dense chemotherapy, which has been reported to improve survival in patients with breast cancer.^{5,6} Pegfilgrastim administration is associated with little toxicity except for bone pain.⁷ In early clinical trials, the incidence of pegfilgrastim-induced

bone pain was reported in 26% to 37% of patients, with fewer than 5% of patients reporting severe pain.^{8,9} In clinical practice, the incidence of pain seems to be significantly higher. Kirshner et al¹⁰ reported an overall incidence of 59% of patients reporting pain, with 24% of patients experiencing severe bone pain (pain greater than 5 on a 10-point scale). In that study,¹⁰ we were unable to identify any risk factors that would predict the occurrence of pain. Patients tried a number of analgesics; nonsteroidal anti-inflammatory drugs (NSAIDs) seemed to provide the most relief.

Pegfilgrastim-induced bone pain is a significant clinical problem. It could lead to discontinuing the growth factor that could reduce chemotherapy dose intensity, possibly decreasing curability. Based on the preliminary work of Kirshner et al,¹⁰ the University of Rochester Cancer Center Community Clinical Oncology Program Research Base designed a phase III, double-blind, placebo-controlled randomized trial to determine whether the NSAID, naproxen, could prevent or decrease the incidence and/or the severity of this pegfilgrastim-induced bone pain. We also wanted to more accurately determine the true incidence of this toxicity in a large number of patients treated in various clinical practices across the country and determine if there were any clinical factors that predicted the development of pain and the efficacy of preventive measures.

PATIENTS AND METHODS

Study Participants

Eligible patients were 18 years or older, able to understand English, had a diagnosis of nonmyeloid cancer, and were scheduled for their first dose of pegfilgrastim on day 2, 3, or 4 of their chemotherapy cycle. All patients gave written, informed consent. The Institutional Review Boards of University of Rochester Cancer Center and all participating Community Clinical Oncology Programs approved the protocol.

Exclusion criteria included active gastrointestinal bleeding, a history of such, or a history of gastric or duodenal ulcers; heart surgery within the past 6 months; allergy to NSAIDs or aspirin; a creatinine level greater than 1.5 times the upper limit of normal; or pregnancy or nursing. Patients could not be taking any NSAID or therapeutic dose of aspirin or warfarin to be eligible for this study.

Study Medication

Participants were given a bottle containing all of their study medications (16 tablets of naproxen 500 mg or placebo) that they were instructed to take before their dose of pegfilgrastim and continue to take twice per day (morning and evening) for 5 days and for up to 8 days if they were still experiencing pain. Pills were to be taken with food. Naproxen and matching placebo tablets were provided by the Clinical Research Pharmacy at the University of Rochester Cancer Center in coded bottles. The placebo was identical to the naproxen in appearance, smell, and taste.

Study Measures

All potentially eligible patients were approached for study participation before their first dose of pegfilgrastim, at which time their eligibility was confirmed and their consent to be on the study was obtained. At that time, patients completed baseline questionnaires, including questions concerning the presence, location, and duration of any bone or joint pain and the manner in which the pain was treated. Patients were given a second set of questionnaires at the time of pegfilgrastim administration. These questionnaires were completed at home and mailed back to the site's study coordinator, who telephoned each patient with a reminder to complete the questionnaire. The second set of questionnaires included questions on the development of any new bone or joint pain; its location, onset, duration, and severity; and an assessment of the efficacy of the assigned medication. Any additional analgesia (prescription and nonprescription) taken by the patient was recorded along with the efficacy of such measures.

Any serious adverse events (SAEs) were identified using the National Cancer Institute's Common Terminology Criteria for Adverse Events (Version 4) and were reported to local investigators and to the University of Rochester Cancer Center Community Clinical Oncology Program Research Base. We tracked the occurrence and severity of toxicity from the medication using the SAE reports submitted to the University of Rochester Cancer Center Research Base. Other less serious adverse events may have occurred but were not required to be reported in this study. Patients also recorded symptoms (ie, pain [other than bone], trouble falling or staying asleep, fatigue, weakness or loss of muscle strength, drowsiness, feeling distressed, heartburn, abdominal pain, nausea, constipation, shortness of breath, or dizziness) on a standard symptom inventory.^{11,12}

Statistical Considerations and Analyses

The primary outcome measure in this double-blind placebo-controlled randomized clinical trial was the area under the curve (AUC) using the trapezoidal quadrature method for bone pain from day 1 through day 5, (day 1, the day pegfilgrastim was administered). AUC can range from 0 to 40. In a daily diary, the patients recorded daily pain severity on a scale of 0 (no pain) to 10 (pain as bad as you can imagine) for the last 24 hours. Any rating of bone pain from 1 to 10 was considered a day with pain. Peak pain was defined as the maximum pain rating over the 5 days. The severity and the duration of the pain were also measured in patient diaries (Fig 1, CONSORT diagram; Fig 2).

Preliminary data from the Hematology/Oncology Associates of Central New York,¹⁰ showed that the average AUC was 5.02 and the standard deviation was 7.64. To have 80% power to detect a difference of 2.51 for the two treatment groups (a 50% reduction of the pain in the treatment

Fig 1. CONSORT diagram.

Fig 2. Study schema. SC, subcutaneously.

group v pain in the control group) using a two-sided test with significance level of .05, we required at least 145 evaluable patients in each treatment group, thus 290 evaluable patients in total. In this multicenter trial, our study closing date was based on when we expected to reach our target accrual of evaluable participants.

Potential risk factors for the development of pegfilgrastim-induced bone pain as well as for response or failure to respond to the assigned treatment were analyzed. These factors included participant age, sex, ethnicity, disease and stage, and chemotherapeutic regimens.

The primary outcome analysis was a two-sample *t* test of AUC (equal variances assumed). We also performed a *t* test on peak pain. Because the AUC and peak pain distributions were moderately skewed, we also performed a Wilcoxon rank sum test. From the bone pain item in patients' daily diaries, when patients were asked to rate their level of pain, we defined "no pain" as any instances in which patients scored their pain 0, and "any pain" for all other responses. Severe pain was similarly defined as any bone pain score greater than 5. Contingency tables with arm were tabulated for both pain measures and likelihood ratio tests were used to evaluate the independence of the variables in these tables.

Subgroup analysis to suggest differential responses to the drug was performed on any pain and AUC using the available demographic characteristics. However, some of the characteristics could not be used because of their distributions. For tumor type, for example, breast cancer was dominant, with small percentages for gynecologic, hematologic, or lung cancers. We restricted our attention to gender, white/nonwhite, marital status, education, and previous chemotherapy. Age was represented as ≥ 65 years versus younger than 65 years. Logistic regression was used to study any pain and multiple regression analysis was used to study AUC. To achieve the most parsimonious models, variance inflation factors were inspected to identify variables that were highly intercorrelated (variance inflation factor > 4). None were found. Then, a backward-stepwise variable selection process was used to remove insignificant variables based on the .10 significance level.

In addition, use of pain medications for more than 5 days was summed for each prescription and nonprescription medication. Comparisons between drug and placebo were performed using a Wilcoxon rank sum test.

RESULTS

From June 2008 to June 2009, 510 patients were entered onto the study; 257 received naproxen and 253 received placebo (Table 1). The baseline characteristics were equivalent between the two treatment groups. The majority of patients were female (86%) and white (89%). Breast cancer accounted for 67% of the malignancies and lung cancer for 10%. Figure 1 delineates the dropout rate and patients who could

not be analyzed. Of 257 patients randomly assigned to the naproxen group, 232 were analyzed. Of the 253 patients randomly assigned to the placebo group, 229 were analyzed.

The mean AUC was 6.04 (95% CI, 4.94 to 7.14) for the naproxen group and 7.71 (95% CI, 6.59 to 8.84) for the placebo group, a 22% reduction from the use of naproxen. The difference of 1.67 (95% CI, 0.10 to 3.24) was significant ($P = .037$). The Wilcoxon rank sum test also showed significance ($P = .007$). Similarly, the mean peak pain was 2.59 (95% CI, 2.20 to 2.97) for the naproxen group and 3.40 (95% CI, 2.98 to 3.81) for the placebo group, a 24% reduction from the use of naproxen. The difference of 0.810 (95% CI, 0.25 to 1.37) was also statistically significant ($P = .005$.) This distribution was also skewed and the Wilcoxon rank sum test yielded $P = .004$. Bone pain generally reached a maximum at about 3 days. The effect of naproxen was present throughout all 5 days, with the maximum benefit around 3 days (Fig 3).

Contingency table analysis of any pain and severe pain revealed that the naproxen group showed improvement, with any pain decreasing from 71.3% to 61.1% ($P = .020$), a 10% reduction. Naproxen also reduced overall pain duration from 2.40 to 1.92 days ($P = .009$). Severe pain reduction showed a similar decrease from 27.0% to 19.2% ($P = .048$; Table 2).

From the subgroup analysis, we found that only African American patients experienced more bone pain than white patients (African American patients, 10.2; 95% CI, 7.08 to 13.32 v white patients, 6.48; 95% CI, 5.69 to 7.28). There was no differential effect of drug treatment (no dependency on naproxen/placebo arm; AUC, $P = .76$; any pain, $P = .88$) between white patients and African Americans.

Pain medication usage was assessed over the 5 days of the study. Those patients receiving the study drug took an average of 1.03 prescription pain medications while on study, whereas those in the placebo group took an average of 1.81 prescription pain medications ($P < .05$; Table 3), a 43% reduction. The average number of nonprescription pain medications taken over the 5 days was 3.54 in the naproxen group and 4.11 in the placebo group ($P < .05$; Table 3), a 14% reduction.

There were 12 reported SAEs. Six SAEs occurred in patients receiving naproxen and six occurred in patients receiving placebo; all of these were either unlikely or unrelated to the intervention. We

Table 1. Demographics and Baseline Clinical Characteristics of the Naproxen- and Placebo-Randomized Groups

Demographic or Clinical Characteristic	Naproxen (n = 257)		Placebo (n = 253)		All (N = 510)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sex						
Female	222	86	215	85	437	86
Male	35	14	38	15	73	14
Race						
African American	14	5	19	8	33	6
Asian	8	3	6	2	14	3
White	228	89	227	90	455	89
Other	7	3	1	0	8	2
Tumor type						
Breast	175	68	166	66	341	67
Gynecologic	16	6	13	5	29	6
Hematologic	18	7	17	7	35	7
Lung	22	9	31	12	53	10
Other	26	10	24	10	50	10
Marital status						
Married	181	72	179	71	360	71
Not married	72	28	72	29	144	29
Education						
Some college	180	71	164	65	344	68
High school or less	73	29	87	35	160	32
Previous tamoxifen						
Yes	8	3	11	4	19	4
No	245	97	240	96	485	96
Previous chemotherapy						
Yes	60	24	75	30	135	27
No	193	76	176	70	369	73
Previous RT						
Yes	18	7	30	12	48	10
No	235	93	221	88	456	90
Age, years						
Mean	55.6		56.8		56.2	
SE	0.8		0.7		0.5	
Pain at its worst in last 24 hrs (scale, 0-10)						
Mean	1.78		1.87		1.83	
SE	0.14		0.14		0.10	
Bone pain today or during previous 3 days (scale, 0-10)						
Mean	0.47		0.64		0.56	
SE	0.09		0.10		0.07	

Abbreviations: Hrs, hours; RT, radiation therapy.

assessed symptoms in all participants using a standard symptom inventory and found no significant associations between symptoms in the naproxen group compared with the placebo group, with the exception of both abdominal pain and sleep, which were significantly improved in the naproxen group ($P < .01$).

DISCUSSION

Pegfilgrastim-induced bone pain is a significant clinical problem. Although sometimes mild in nature, this bone pain can be quite severe for many and may result in discontinuation of pegfilgrastim, which could jeopardize adequate dosing of chemotherapy. We found in our phase III double-blind placebo-controlled randomized clinical trial that naproxen significantly reduced pegfilgrastim-induced bone pain by 22% over the whole 5 days of the course, representing an absolute difference of 10%. Naproxen was able to significantly reduce the incidence, severity, and duration of pegfilgrastim-induced bone pain.

Initial reports of the incidence of pegfilgrastim-induced bone pain ranged from 26% to 37%, with approximately 5% of patients experiencing severe pain.^{8,9} However, we found in one of our large clinical practices an incidence of 59% of patients experiencing pain, with 24% of patients experiencing severe pain (defined as greater than 5 on a scale of 1 to 10).¹⁰ In our study, 71.3% of patients treated with placebo experienced some pain, with 27.0% reporting severe pain greater than 5 on a 0 to 10 scale. The frequency of pegfilgrastim-induced bone pain in our study is also higher than that in initial reports and likely a more accurate reflection of what oncologists see in clinical practice. It is also possible that patients entering a pain-prevention study are more likely to be aware of and record even minor pains. Of note is the fact that in our study patients self-reported their pain using a scale of 0 to 10. In earlier studies,^{8,9} investigators reported the pain, using the Common Terminology for Adverse Events grade 0 to 4 scale.

Fig 3. (A) Mean bone pain by day. Mean across patients and 95% CIs for daily bone pain, down by day and arm, on a scale of 0 to 10. Day 1 denotes the day of pegfilgrastim injection. (B) Area under the curve (AUC) distributions. Notched box plots of AUC for bone pain. Nonoverlapping notches indicate a statistically significant difference in the medians. (C) Mean AUC bone pain. Mean and 95% CIs for the average AUC. The possible range of AUC in (B) and (C) is 0 to 40.

The primary goal of our study was to determine if the NSAID, naproxen, could prevent or ameliorate pegfilgrastim-induced bone pain. To that end, this was a positive study. There was a statistically significant decrease in the percentage of patients who experienced any pain (71.3% to 61.1%). Of even greater impact was the significant decrease in severe pain (score, > 5 on a scale of 1-10), which is often debilitating and can lead to discontinuation of pegfilgrastim. Naproxen decreased the incidence of severe pain from 27.0% to 19.2%. Moreover, the primary parameter of the study, AUC for pain and duration, showed a statistically significant improvement resulting from the naproxen (mean AUC decreasing from 7.71 to 6.04). In practical terms, per the results of our study, if 100 patients were treated with naproxen, 10 would benefit in terms of preventing pegfilgrastim-induced bone pain; 29 would never have experienced any pain at all, regardless of any preventive treatment; and 61 patients would have still experienced pain, despite the naproxen.

In terms of severe pain (score, > 5 on a scale from 0 to 10), if 100 patients were treated with naproxen, eight patients would benefit in terms of preventing severe pain, 73 would have never experienced severe pain, and 19 would have still had severe pain. Naproxen is a relatively inexpensive drug with few serious adverse events when given to this population of patients. In future trials, the issue of overall toxicity from preventive agents needs to be further addressed.

We were unable to identify any clinical risk factors for the development of pegfilgrastim-induced bone pain. These included age, sex, type of cancer, and treatment. In an exploratory analysis, the incidence of pegfilgrastim-induced bone pain was higher in black patients than nonblack patients, but the numbers for this analysis were small. No clinical factors were able to predict response to naproxen.

In summary, our study confirms the relatively high incidence of pegfilgrastim-induced bone pain in the clinical oncology setting. Naproxen decreased the incidence, duration, and severity of pegfilgrastim-induced bone pain. Even with this preventive treatment, more than 60% of patients still experienced some pain. For 19%

Table 2. Contingency Table Analyses of Naproxen Versus Placebo for Any Pain Versus No Pain and Any Severe Pain Versus No Severe Pain

Pain Level	Naproxen		Placebo		P
	No. of Patients	%	No. of Patients	%	
No pain v pain					.020
No pain	91	38.9	66	28.7	
Pain	143	61.1	164	71.3	
No severe pain v severe pain					.048
No severe pain	189	80.8	168	73.0	
Severe pain	45	19.2	62	27.0	

Table 3. Total Rx and Non-Rx Pain Medication Usage Over Days 1-5

Study Arm	No. of Patients	Mean	SD	Range
Rx				
Drug	233	1.03	3.22	0-22
Placebo	230	1.81	5.60	0-70
Non-Rx				
Drug	233	3.54	9.00	0-110
Placebo	231	4.11	6.27	0-42

Abbreviations: Non-Rx, nonprescription; Rx, prescription; SD, standard deviation.

of patients the pain was severe, indicating a need to develop better strategies to prevent and/or treat pegfilgrastim-induced bone pain. Future trials of naproxen or other agents to prevent pegfilgrastim-induced bone pain are needed.

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Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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