Published in final edited form as:

Support Care Cancer. 2016 July ; 24(7): 3085–3093. doi:10.1007/s00520-016-3119-0.

Randomized phase II study of loratadine for the prevention of bone pain caused by pegfilgrastim

J. Moukharskaya[1], **D.M. Abrams**[2], **T. Ashikaga**[3], **F. Khan**[4], **J. Schwartz**[5], **K. Wilson**[4], **C. Verschraegen**[4], **T. Openshaw**[6], **J. Valentine**[7], **J. Eneman**[8], **P. Unger**[9], and **S. Ades.**[4]

[1]Harold Alfond Center for Cancer Care, Maine General Health, Augusta, ME

[2]Hematology/Oncology, Harrison Health Partners, Poulsbo, WA

[3]Medical Biostatistics, University of Vermont, Burlington, VT

[4]University of Vermont Cancer Center, Burlington, VT

[5]Albany College of Pharmacy and Health Sciences, Vermont Campus, Colchester, VT

[6]Eastern Maine Medical Center Cancer Care of Maine, Bangor, ME

[7]Central Vermont Medical Center, Barre, VT

[8]York Hospital Oncology and Infusion Center, York, ME

[9]Champlain Valley Hematology Oncology, Colchester, VT

Abstract

Purpose—Bone pain is a common side-effect of pegfilgrastim and can interfere with quality of life and treatment adherence. This study i nvestigated the impact of antihistamine prophylaxis on pegfilgrastim-induced bone pain.

Methods—This is a two stage enrichment trial design. Patients receiving an initial dose of pegfilgrastim after chemotherapy were enrolled into the observation stage (OBS). Those who developed significant back or leg bone pain (SP) were enrolled into the treatment stage (TRT) and randomized to daily loratadine 10 mg or placebo for 7 days. SP was defined by Brief Pain Inventory as back or leg pain score ≥ 5 and a 2 point increase after pegfilgrastim. The primary end-point of TRT was reduction of worst back or leg bone pain with loratadine, defined as 2 point decrease after treatment compared to OBS.

Results—213 patients were included in the final analysis. Incidence of SP was 30.5%. The SP subset had a worse overall Functional Assessment of Cancer Therapy – Bone Pain score (33.9 vs. 51.7, $p < 0.001$) and a higher mean white blood cell count (15.4 vs. 8.4 K/cm^3, $p = 0.013$) following pegfilgrastim than those without SP. 46 patients were randomized in the TRT. Benefit was 77.3% with loratadine and 62.5% with placebo ($p = 0.35$). Baseline NSAID use was

Correspondence to: Steven Ades, MD MSc, University of Vermont Cancer Center, Division of Hematology and Oncology, Department of Medicine, Given Building, E214C, 89 Beaumont Ave, University of Vermont, Burlington, VT 05405 USA, Tel: 1-802-656-5487, steven.ades@uvm.edu.

Conflict of Interest: The authors declare that they have no conflict of interest or financial relationship with the organization that sponsored the research. The authors have had full control of all primary data, and agree to allow the journal to review their data if requested.

documented in 4 patients (18.2%) in loratadine arm and 2 patients (8.3%) in placebo arm, with baseline non-NSAID use documented in 5 (22.7%) and 6 (25%) patients respectively. Eight additional patients used NSAIDS by day 8 compared to day 1 (6 in the loratadine and 2 in the placebo arm). A total of 6 additional patients used non-NSAIDS by day 8 compared to day 1 (4 in the loratadine and 2 in the placebo arm).

Conclusions—Administration of prophylactic loratadine does not decrease the incidence of severe bone pain or improve quality of life in a high-risk patient population.

Keywords

pegfilgrastim; bone pain; prophylaxis; antihistamine; loratadine; taxane

INTRODUCTION

Filgrastim (G-CSF) is a recombinant hematopoietic myeloid growth factor that selectively stimulates the proliferation and differentiation of neutrophil precursors. Pegfilgrastim is a 20-kilodalton polyethylene glycol carrier of filgrastim that is covalently bound at the N-terminal residue. Randomized trials have demonstrated that a single dose of pegfilgrastim offers neutrophil support comparable to multiple once-daily doses of filgrastim (1, 2). G-CSF and pegfilgrastim are used to reduce infection risk associated with neutropenia and febrile neutropenia in patients receiving myelosuppressive chemotherapy (3). They can also be administered prophylactically to maintain chemotherapy intensity or dose-density. The most common adverse event of G-CSF and pegfilgrastim is bone pain with an overall incidence of 36 to 70% in cancer patients (4-6). The pain, which is primarily located in the back and legs, generally appears within 2 days of pegfilgrastim administration and lasts for 2-4 days (7). This pain can be controlled with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, corticosteroids, and opioids. Only naproxen has been studied in a randomized trial. Prevention with this agent reduces incidence and severity of pegfilgrastim-induced bone pain, but over 60% of patients still experienced some pain (4).

No patient risk factors have been identified that are predictive for pegfilgrastim-induced pain (4, 8) and the exact mechanisms of G-CSF-induced pain have yet to be elucidated. Possible pathways include bone marrow expansion, peripheral nociceptor sensitization, immune function modulation, and direct effect on bone metabolism (6, 9). G-CSF modulates local and systemic inflammatory responses through histamine, which acts as a chemical mediator of inflammation and local edema (10-12), causing both nociceptive c-fiber-mediated and neuropathic pain (13).

Antihistamines have direct adjuvant analgesic activity (14). Several case reports (15, 16) and a small pilot study (17) have suggested antihistamine efficacy in the prevention of pegfilgrastim-induced pain. To determine the merits of this strategy, we hypothesized that loratadine, a second generation type 1 antihistamine (18), would decrease the incidence of pegfilgrastim-induced significant back or leg bone pain (SP), and performed a randomized trial in a high-risk population.

PATIENTS AND METHODS

Study design

This is a randomized multicenter phase II enrichment-design study of loratadine versus placebo for pegfilgrastim-induced bone pain. The study included an observation (OBS) stage followed by a treatment (TRT) stage (Figure 1). Subjects were consented if they were to receive pegfilgrastim, 6 mg subcutaneously, for the first time with chemotherapy. Each participant signed an IRB-approved, protocol–specific informed consent in accordance with federal and institutional guidelines. All procedures were in accordance with the ethical standards of local institutional review board and with the 1964 Helsinki declaration and its later amendments.

All consented patients completed screening surveys to determine incidence of pegfilgrastim-induced pain during OBS. Subjects who developed significant pain (SP) were eligible to enter TRT, and were randomized to loratadine 10 mg or a matched placebo daily for 7 days starting on the day of pegfilgrastim administration. Loratadine treatment benefit and the incidence of worst back and leg pain were compared between study arms in TRT patients.

Patient eligibility

Patients 18 years of age or older with an ECOG performance status of 0 to 3, with adequate renal function (estimated CrCl > 30 ml/min) and hepatic function (AST ≤ 2.5 × ULN, ALT ≤ 2.5 × ULN, total bilirubin ≤ 2 .5 × ULN) were eligible for the trial if they had histologically or cytologically documented malignancy and were scheduled to receive pegfilgrastim with two consecutive cycles of the same chemotherapy with at least a 14 day interval between cycles. Patients were excluded if there was a history of hypersensitivity or intolerance to antihistamines or concurrent use of antihistamines during or for 2 days prior to the study period except for a single dose of antihistamine as required for administration of chemotherapy or blood transfusion. Other exclusion criteria were concomitant use of amiodarone or history of prior use of pegfilgrastim or G-CSF.

Analgesic use at baseline was permitted. Rescue use of analgesics during OBS and TRT was recorded and categorized as NSAID vs. non-NSAID (acetaminophen and opioid analgesics). Patients were instructed not to use analgesics prophylactically in the absence of pain or for other indication. CBC results were recorded on day 1 and day 8 of both OBS and TRT.

Randomization

Subjects who developed SP during the OBS were randomized 1:1 to loratadine or placebo, stratified on taxane use. At the time of study initiation, each of 7 participating sites designated a pharmacist who would remain unblinded for the duration of the study to assign new subjects consecutively according to a list of arm assignments that had been randomly ordered based on a block design. All patients, treatment team, and research staff were blinded to treatment status.

Assessments

During both OBS and TRT, bone pain was assessed by standardized questionnaires on day 1 before treatment and on day 8 after the administration of pegfilgrastim, assessing pain experienced during the previous 7 days. Questionnaires during both OBS and TRT were self-administered with research staff available for assistance or clarification if necessary. The Worst Pain (WPS) and Average Pain Scales (APS) of the Brief Pain Inventory and the Functional Assessment of Cancer Therapy – Bone Pain (FACT-BP) for functional effects of pain were used in this study (19, 20). WPS and APS of the Brief Pain Inventory are questionnaires assessing the rate of worst or average back and leg pain, respectively. A higher score reflects higher pain severity (0-10). The questionnaire also contains the front and back diagrams of the entire body, asking the patient to shade the areas of pain. FACT-BP is a 15-item questionnaire, assessing cancer-related bone pain and its effect on quality of life. Each question is answered on a graduated scale (0-4). A lower aggregate score reflects higher bone pain and/or worse quality of life (19).

To be enrolled in TRT, patients had to have back and leg SP based on WPS, defined as a score ≥ 5 on day 8 and a 2-point increase during the 7 days of OBS after pegfilgrastim use. This definition of SP aims to incorporate both severity and change in pain in response to pegfilgrastim. Although not validated in this setting, there is evidence in support of a score of ≥ l as corresponding to moderate pain at minimum, and an absolute change of 2 as meaningful (21, 22). The primary endpoint was benefit from loratadine prophylaxis, defined as a reported decrease in WPS difference from Day 1 to 8 of at least 2 points between OBS and TRT. All sites of bony pain were recorded in the questionnaires in addition to back and legs. Compliance was assessed via Day 8 pill counts during TRT.

Statistical analysis

Descriptive statistics were obtained for all measures. Ordinal and quantitative measures were summarized with means, standard deviations, and ranges supplemented with 95% confidence intervals. Binary data percentages were supplemented with exact 95% confidence intervals using the Clopper-Pearson method while subset comparisons were compared using Fisher’s exact test. Time dependent binary comparisons were examined using McNemar’s approach with exact p-values being based upon a binomial probability model. Within subject comparisons of ordinal and higher measures were based upon a mixed model repeated measures analysis of variance. Subsequent post-hoc comparisons between day 1 and day 8 for both the OBS and TRT were conducted using paired t-tests or Wilcoxon signed rank tests where appropriate. Day 1 and day 8 specific comparisons employed two sample t-tests or Kruskall-Wallis nonparametric testing when needed. Exploratory factor analysis was conducted on the correlation matrix for all reported pain sites using a Varimax rotation to assist in factor loading interpretations with an Eigen value cut-off of 1.0 for factor extraction.

The primary outcome comparison between the two randomized treatment arms used an intent to treat approach and was made using the Fisher’s exact test and a 5% Type I error level. A target sample size of 55 patients for the TRT of the trial was based on the following assumptions: 30% incidence of SP during the OBS, a 10% benefit with placebo compared to

a 50% benefit with loratadine for the randomized TRT and a 89% power using a non-directional chi-square test with a 5% Type I error level. Statistical calculations and data management were conducted using SYSTAT (ver. 11) and StatXact (ver. 4.0).

RESULTS

The study was conducted at seven sites in VT, NY, and ME. Between February of 2011 and December of 2013, 227 patients were enrolled in the OBS, 213 of whom were included in the final analysis. Fourteen patients provided incomplete responses to pain questionnaires. The CONSORT flow diagram is shown in Figure 1, and baseline demographic and clinical variables are provided in Table I.

Observation Stage (OBS)

Impact of pegfilgrastim on bone pain incidence—SP occurred in 30.5% (65/213, CI: 24.4% - 37.2%). In the entire cohort, the average WPS scores increased from 1.6 (CI: 1.4-2.1) at baseline to 3.6 (CI: 3.1-4.0) during the 8 days following the administration of the pegfilgrastim ($p<0.001$). In particular, there were 111 cases where WPS scores were greater at follow-up on day 8 compared to their day 1 baseline, in contrast to only 27 cases with the opposite trend. Figure 2 depicts the distribution of the severity of bone pain before and after pegfilgrastim administration, and shows a shift to higher pain intensity after treatment.

Compared to the subset without SP at day 8, those with SP had a worse overall score on the FACT-BP questionnaire reflecting the increase in bone pain and its effect on quality of life. At day 8 of OBS, the subset with SP also had a higher number of painful sites, and higher intensity of both WPS and APS (Table II). Patients with SP had significantly higher prevalence of pain at day 8 at several sites including shoulders, back, hips and legs, compared those without SP at day 8 (Figure 3). Exploratory factor analysis indicated that patients in the SP group were more likely to experience pain at day 8 in 3 contiguous areas of the body including A) head, sternum and ribs, B) neck, shoulder, and upper back, C) upper and lower legs.

Younger patients (≤ 59 years) were more likely to develop SP than older patients (37.0% vs. 23.8%, $p=0.039$). Gender was not associated with SP development. Patients receiving taxane-containing chemotherapy were more likely to develop SP compared to those who did not (50.8 vs. 23.0%, $p <0.001$). Corresponding WPS means were 1.6 (CI: 1.1 - 2.2) on day 1 and 4.8 (CI: 4.0 - 5.7) on day 8 in those receiving taxanes.

Analgesic use during OBS—Of the 186 patients who provided complete analgesic use records, 31 (16.7%, CI: 11.6%-22.8%) used NSAIDS by day 8 including 21/53 (39.6%, CI: 26.5%-54.0%) of those with SP and only 10/133 (7.5%, CI: 3.7%-13.3%) of those without SP. Corresponding proportions for non-NSAID use at day 8 are 34/53 (64.2%, CI: 49.8%-76.9%) and 41/133 (30.8%, CI: 23.1%-39.4%). Of the 47 patients in the SP subset who were not using NSAID analgesics on day 1, 16 (34.0%, CI: 20.1% - 49.3%) were new users by day 8. This compares to only 4 (3.3%, CI: 0.9% - 8.1%) new users in the 123 patient subset who did not develop SP (OR 15.4, CI: 4.4 - 66.2).

Bone pain and blood counts—Comparison of the mean white blood cell (WBC) and absolute neutrophil counts (ANC) demonstrated significant differences in both WBC and ANC between patients with SP and non-SP on day 8 of OBS. WBC and ANC rose from an average day 1 level of 8.8 (CI: 7.7 – 10.0 K/cm^3) and 6.7 (CI: 5.5 – 7.9 K/cm^3) to 15.4 (CI: 10.4 – 20.4) and 11.6 (CI: 7.5 – 15.6) in the SP subset, respectively. Among those without SP, day 1 mean WBC increased marginally from 7.9 (CI: 6.3 – 9.6 K/cm^3) to 8.4 (CI: 6.4 – 10.5 K/cm^3), with corresponding ANC of 4.6 (CI: 4.1 – 5.1) to 6.9 (CI: 4.9 – 8.8), respectively. The counts at day 8 were significantly greater in the SP compared to non-SP subsets for both WBC (p= 0.013) and ANC (p= 0.039). These results were confirmed by within-subject comparisons between day 1 and day 8 (data not shown).

Treatment Stage (TRT): Efficacy of loratadine

Of the sixty-five (30.5%) of patients who developed SP, 46 were randomized in TRT (22 in loratadine arm, 24 placebo arm) with 1 patient not receiving allocated treatment and 1 lost to follow-up (Figure 1). Compliance with prophylaxis was excellent. Demographic and clinical characteristics of these patients are shown in Table III. Gender, age, malignancy type and taxane use were all similarly distributed in loratadine vs. placebo groups, with the exception of proportion of males which is higher in the loratadine arm (36.4% vs 12.5%). As observed in OBS, taxane therapy caused more frequent SP compared to non-taxane treatment (71.4 vs. 30.4%, p = 0.015) in TRT. A total of 8 additional patients used NSAIDS by day 8 compared to day 1 (6 in the loratadine group and 2 in the placebo group). A total of 6 additional patients used non-NSAIDS by day 8 compared to day 1 (4 in the loratadine group and 2 in the placebo group) (Table III).

The primary end point of the randomized TRT was analgesic benefit from loratadine prophylaxis. In the intent-to-treat population, the rate of benefit was 17/22 (77.3%, CI: 54.6% - 92.2%) in the loratadine arm and 15/24 (62.5%, CI: 40.6% - 81.2%) in the placebo arm (p=0.35). In the loratadine arm, WPS scores climbed from 1.9 (CI: 0.8-3.1) to 4.7 (CI: 3.46-6.1) with pegfilgrastim therapy. Corresponding WPS levels in the placebo arm were 2.5 (CI: 1.1-3.9) and 4.6 (CI: 3.1-6.0), respectively. Eleven patients in each arm developed SP.

An exploratory subset analysis of the primary outcome in the subset receiving taxane-containing chemotherapy revealed that 10/11 (90.9%) met the primary endpoint from loratadine prophylaxis compared to only 3/11 (27.3%) in the placebo arm (p=0.008). However, taxane therapy was associated with increase in WPS scores after pegfilgrastim regardless of whether a patient received loratadine (1.73 increased to 5.00, p <0.001) or placebo (1.70 increased to 6.00, p=0.007).

Treatment stage: quality of life

For patients in TRT, analysis of the data showed no significant difference between day 1 FACT-BP scores between study arms (p = 0.330), or change in mean FACT-BP scores between the time before and after pegfilgrastim use within each arm. In the loratadine group mean FACT-BP score was 50.7 (CI: 44.5–55.9) at baseline and 48.1 (CI: 43.7–52.5) at day 8 (p=0.416). Corresponding scores in the placebo group were 46.8 (CI: 40.6–53.1) and 47.9 (CI: 44.0–51.7) (p=0.677).

DISCUSSION

Pegfilgrastim-induced bone pain is common and can interfere with a patient's quality of life and treatment adherence. This study was designed as a randomized phase II trial to (i) characterize the nature and extent of bony pain associated with pegfilgrastim therapy, and (ii) investigate the impact of antihistamine prophylaxis on SP. The two-stage enrichment design allowed the selection of patients with severe pain, while excluding the patients with mild to moderate pain. There are many definitions of severe bone pain in the literature. Reports have used CTCAE grading, classification into mild/moderate/severe categories, or use of the WPS of the Brief Pain Inventory, leading to differences in reported incidence of pain (4, 5, 23). In this study, we defined severe pain as a WPS score of ≥5 to capture a population with moderate to severe pain, and we controlled for baseline pain.

Analysis of the OBS data answered several important questions, including the observation of a 30.5 % incidence of pegfilgrastim-induced SP and positive correlation between the pain severity and the use of taxanes. The most common sites of pegfilgrastim-induced pain were back, legs, and hips. Participants with severe bone pain had an inferior quality of life per FACT-BP aggregate score. The incidence of SP in our study is consistent with a 27.0 % incidence in the placebo group of a randomized study of naproxen vs. placebo (4), using a similar definition of severe pain as a score of 5 on the WPS but without adjustment for baseline pain. In contrast, a recent study of 2408 first-time stem cell donors receiving high-dose G-CSF revealed that over 80% of donors experienced bone pain by day 4 of therapy, but only 9% characterized their bone pain as severe (24). Similar to our own results, the stem cell donor cohort reported bone pain most often in the axial skeleton, especially the back, hips, and pelvis (24).

There was a positive correlation between pain severity and the elevation of WBC and ANC counts. These laboratory marker variations may be related to the pathophysiology of pegfilgrastim-induced pain, which includes bone marrow expansion (6). To our knowledge, there are no previous reports regarding the correlation between the severity of pegfilgrastim-induced bone pain and ANC and WBC counts. If validated, these may serve as biomarkers for development of pegfilgrastim-induced SP.

Loratadine prophylaxis in TRT did not significantly reduce SP compared to placebo in a high risk population. Our results differ from a pilot study demonstrating lower pegfilgrastim-induced pain severity measured as AUC for pain over a 5-day period (17). A randomized phase 2 study comparing prophylactic naproxen and loratadine in breast cancer subjects is closed to accrual but not reported (25). Reasons for differing results can be found in inherent limitations in our trial. One limitation of this study design was that participants were permitted to use analgesics for bone or other pain. Use of these agents was captured on the questionnaires and there were differences between arms in the use of both NSAID and non-NSAID analgesia, although numbers are too small for adjustment. A second potential limitation is the reliance upon a questionnaire (FACT-BP) that is validated for use in chronic rather than transient bone pain. It was also administered only at two time points during 2 cycles of chemotherapy, relying on patient recall of their pain experience. We also used a definition of SP with a lower pain threshold of 5/10, which may have included patients with

less than severe pain. Another limitation is the small sample size for OBS. Lastly, there is evidence in the literature that G-CSF-induced bone pain improves with subsequent cycles (5, 26), which may dilute a potential benefit with prophylaxis. In our study only 11 patients in the placebo arm (47.8%) developed SP in TRT, confirming this observation.

Randomization was stratified by the use of taxane-based chemotherapy given the expected association between use of this class of agents and both arthralgias and myalgias (27). Antihistamines are reported to relieve taxane-induced arthralgias and myalgias (27, 28). Pegfilgrastim use is also associated with joint and muscle pain along with classic bone pain (23). Although the questionnaire focused on global bone pain independently of cause, taxane therapy was associated with more frequent pegfilgrastim-induced SP compared to non-taxane treatments in both stages of this trial. An exploratory analysis demonstrating that 90.9% of patients receiving taxane-containing chemotherapy benefited from loratadine prophylaxis compared to only 27.3% in the placebo arm ($p = 0.008$) may in part reflect effective loratadine prophylaxis of taxane-induced pain.(5, 24)

This study demonstrated that prophylactic administration of the antihistamine loratadine at standard dose does not decrease the incidence of significant pegfilgrastim-induced bone pain or improve quality of life in patients at higher risk of developing pain, but subsequent elevation of the neutrophil count following pegfilgrastim is correlated with higher incidence of severe bone pain. While current evidence does not support the use of loratadine for bone pain, future clinical trials with a larger population receiving taxanes should address the possibility of efficacy in this particular group.

Acknowledgments

We want to remember Dr. Steven Grunberg, who was a key original investigator in the conception and drafting of the study design and protocol before his untimely passing in 2013. His leadership and vision in the field of supportive care in cancer has been an inspiration to all investigators who participated in this study and the broader oncology community in Northern New England.

Support: This project was supported by Award Number 2U10CA037447 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. ClinicalTrials.gov identifier: NCT01311336.

The following institutions participated in the study:

1. University of Vermont Cancer Center, Burlington, VT

2. Central Vermont Medical Center, Barre, VT

3. Champlain Valley Hematology Oncology, Colchester, VT

4. C.R. Wood Cancer Center at Glens Falls Hospital, NY

5. New England Oncology Specialists, ME

6. York Hospital Oncology and Infusion Center, York, ME

7. Eastern Maine Medical Center Cancer Care of Maine, Bangor, ME

References

1. Holmes FA, O'Shaughnessy JA, Vukelja S, Jones SE, Shogan J, Savin M, Glaspy J, Moore M, Meza L, Wiznitzer I, Neumann TA, Hill LR, Liang BC. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002; 20:727–31. [PubMed: 11821454]
2. Vose JM, Crump M, Lazarus H, Emmanouilides C, Schenkein D, Moore J, Frankel S, Flinn I, Lovelace W, Hackett J, Liang BC. Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003; 21:514–9. [PubMed: 12560443]
3. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006; 24:3187–205. [PubMed: 16682719]
4. Kirshner JJ, Heckler CE, Janelsins MC, Dakhil SR, Hopkins JO, Coles C, Morrow GR. 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. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012; 30:1974–9. [PubMed: 22508813]
5. Kubista E, Glaspy J, Holmes FA, Green MD, Hackett J, Neumann T, Pegfilgrastim Study G. Bone pain associated with once-per-cycle pegfilgrastim is similar to daily filgrastim in patients with breast cancer. Clinical breast cancer. 2003; 3:391–8. [PubMed: 12636878]
6. Lambertini M, Del Mastro L, Bellodi A, Pronzato P. The five "Ws" for bone pain due to the administration of granulocyte-colony stimulating factors (G-CSFs). Critical reviews in oncology/hematology. 2014; 89:112–28. [PubMed: 24041627]
7. Crawford J. Safety and efficacy of pegfilgrastim in patients receiving myelosuppressive chemotherapy. Pharmacotherapy. 2003; 23:15S–9S. [PubMed: 12921218]
8. Tigue CC, McKoy JM, Evens AM, Trifilio SM, Tallman MS, Bennett CL. Granulocyte-colony stimulating factor administration to healthy individuals and persons with chronic neutropenia or cancer: an overview of safety considerations from the Research on Adverse Drug Events and Reports project. Bone marrow transplantation. 2007; 40:185–92. [PubMed: 17563736]
9. Bennett A. The role of biochemical mediators in peripheral nociception and bone pain. Cancer surveys. 1988; 7:55–67. [PubMed: 2898291]
10. Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. Nature reviews Immunology. 2008; 8:533–44.
11. Konig B, Konig W. Effect of growth factors on Escherichia coli alpha-hemolysin-induced mediator release from human inflammatory cells: involvement of the signal transduction pathway. Infection and immunity. 1994; 62:2085–93. [PubMed: 7513312]
12. Stosser S, Schweizerhof M, Kuner R. Hematopoietic colony-stimulating factors: new players in tumor-nerve interactions. Journal of molecular medicine. 2011; 89:321–9. [PubMed: 21079906]
13. Baron R, Saguer M. Postherpetic neuralgia. Are C-nociceptors involved in signalling and maintenance of tactile allodynia? Brain : a journal of neurology. 1993; 116(Pt 6):1477–96. [PubMed: 8293282]
14. Rumore MM, Schlichting DA. Clinical efficacy of antihistaminics as analgesics. Pain. 1986; 25:7–22. [PubMed: 2872645]
15. Gudi R, Krishnamurthy M, Pachter BR. Astemizole in the treatment of granulocyte colony-stimulating factor-induced bone pain. Annals of internal medicine. 1995; 123:236–7.

16. Romeo C, Li Q, Copeland L. Severe pegfilgrastim-induced bone pain completely alleviated with loratadine: A case report. Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners. 2015:21.
17. Kirshner JJ, Heckler E, Tiffany S, Reichel C, McAuliffe C, Morrow GR. A phase II study of loratadine to prevent pegfilgrastim-induced pain. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011:29. [PubMed: 27958025]
18. Holdcroft C. Terfenadine, astemizole and loratadine: second generation antihistamines. The Nurse practitioner. 1993; 18:13–4.
19. Broom R, Du H, Clemons M, Eton D, Dranitsaris G, Simmons C, Ooi W, Cella D. Switching breast cancer patients with progressive bone metastases to third-generation bisphosphonates: measuring impact using the Functional Assessment of Cancer Therapy-Bone Pain. Journal of pain and symptom management. 2009; 38:244–57. [PubMed: 19364633]
20. Cleeland CS. The measurement of pain from metastatic bone disease: capturing the patient's experience. Clinical cancer research : an official journal of the American Association for Cancer Research. 2006; 12:6236s–42s. [PubMed: 17062707]
21. Farrar JT. What is clinically meaningful: outcome measures in pain clinical trials. The Clinical journal of pain. 2000; 16:S106–12. [PubMed: 10870749]
22. Li KK, Harris K, Hadi S, Chow E. What should be the optimal cut points for mild, moderate, and severe pain? Journal of palliative medicine. 2007; 10:1338–46. [PubMed: 18095813]
23. Leung M, Florendo J, Kano J, Marr-Del Monte T, Higgins B, Myers R, Menon T, Jones G. A modified filgrastim regimen does not reduce pain burden compared to pegfilgrastim in women receiving chemotherapy for non-metastatic breast cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2015; 23:1669–77. [PubMed: 25421443]
24. Pulsipher MA, Chitphakdithai P, Logan BR, Shaw BE, Wingard JR, Lazarus HM, Waller EK, Seftel M, Stroncek DF, Lopez AM, Maharaj D, Hematti P, O'Donnell PV, Loren AW, Leitman SF, Anderlini P, Goldstein SC, Levine JE, Navarro WH, Miller JP, et al. Acute toxicities of unrelated bone marrow versus peripheral blood stem cell donation: results of a prospective trial from the National Marrow Donor Program. Blood. 2013; 121:197–206. [PubMed: 23109243]
25. NCT01712009. Randomized, Phase 2 Study to Estimate the Effect of Prophylactic Intervention With Naproxen or Loratadine On Bone Pain in Breast Cancer Subjects Receiving Chemotherapy and Pegfilgrastim
26. Gregory S, Schwartzberg L, Mo M, Sierra J, Vogel C. Evaluation of reported bone pain in cancer patients receiving chemotherapy in pegfilgrastim clinical trials: a retrospective analysis. Community Oncology. 2010; 7:297–308.
27. Garrison JA, McCune JS, Livingston RB, Linden HM, Gralow JR, Ellis GK, West HL. Myalgias and arthralgias associated with paclitaxel. Oncology. 2003; 17:271–7. discussion 81-2, 86-8. [PubMed: 12632867]
28. Martoni A, Zamagni C, Gheka A, Pannuti F. Antihistamines in the treatment of taxol-induced paroxystic pain syndrome. Journal of the National Cancer Institute. 1993; 85:676. [PubMed: 8096876]

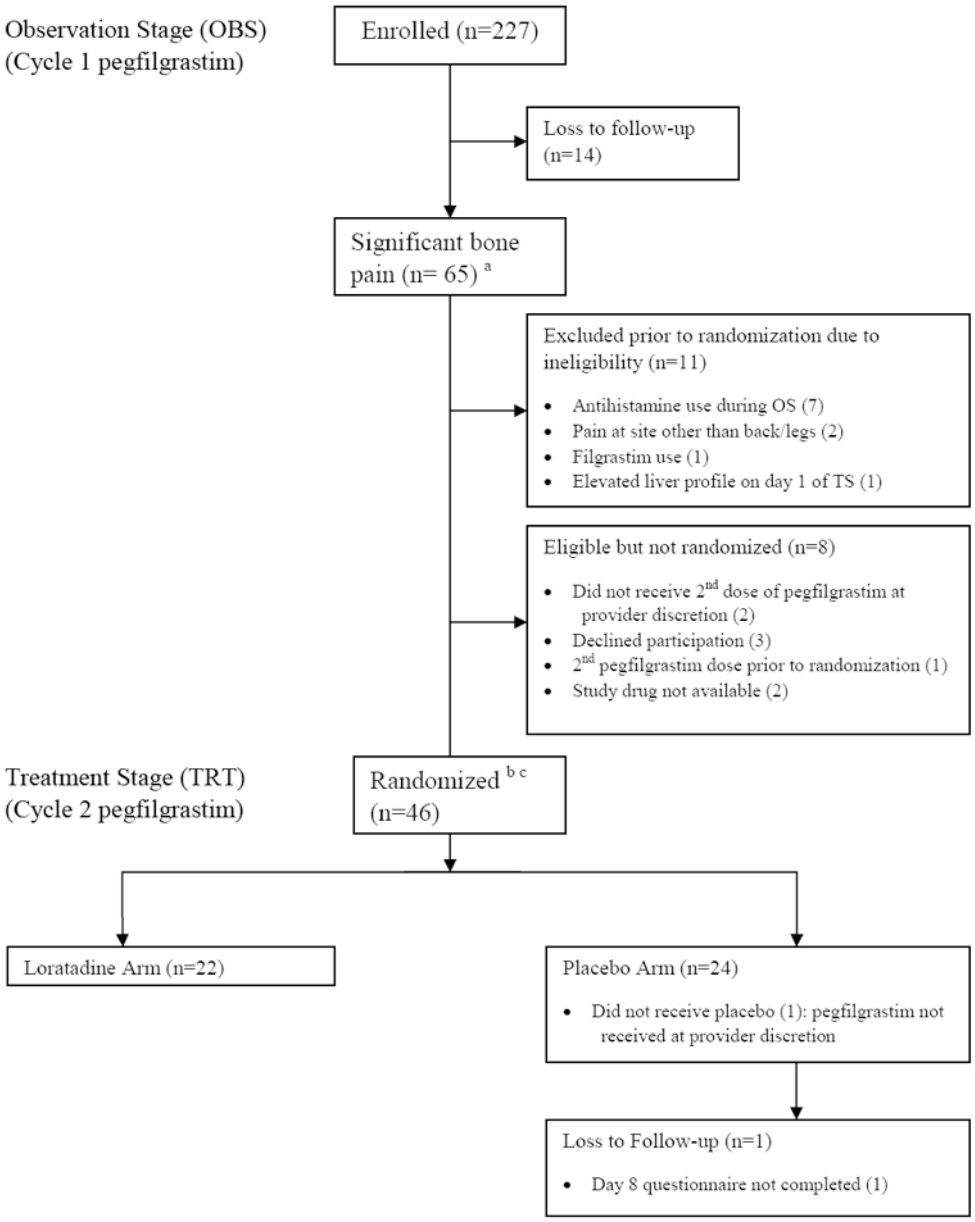

Figure 1. CONSORT

[a] Significant Pain (SP) was defined as a worst back/leg pain score ≥5 by day 8 post chemotherapy and a 2 point increase during the 7 days after pegfilgrastim use, using the Worst Pain Scale (0-10) of the Brief Pain Inventory

[b] Stratification by taxane administration

[c] 3 participants were incorrectly stratified by taxane use

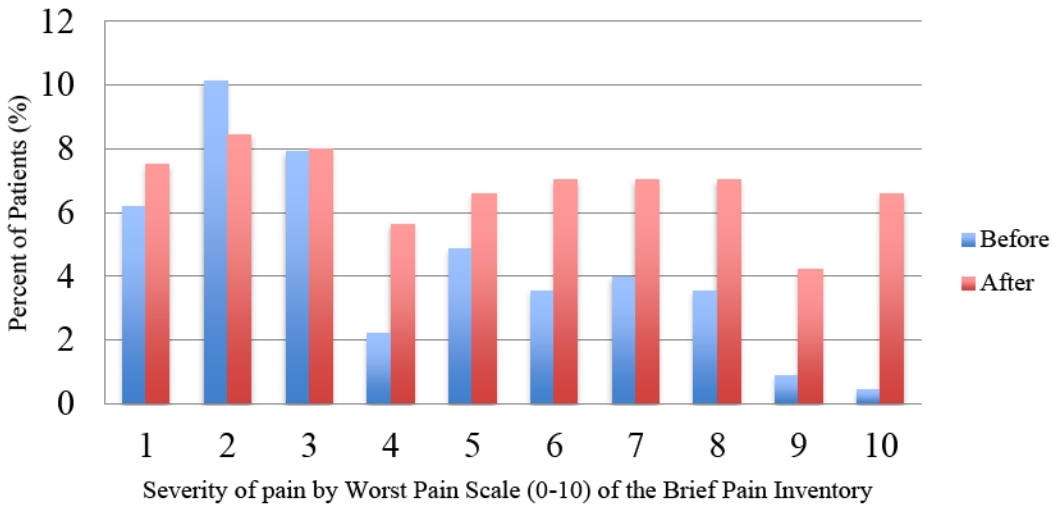

Figure 2.

Severity of bone pain before (day 1) and after (day 8) pegfilgrastim administration during OBS[†].

[†] Observation Stage

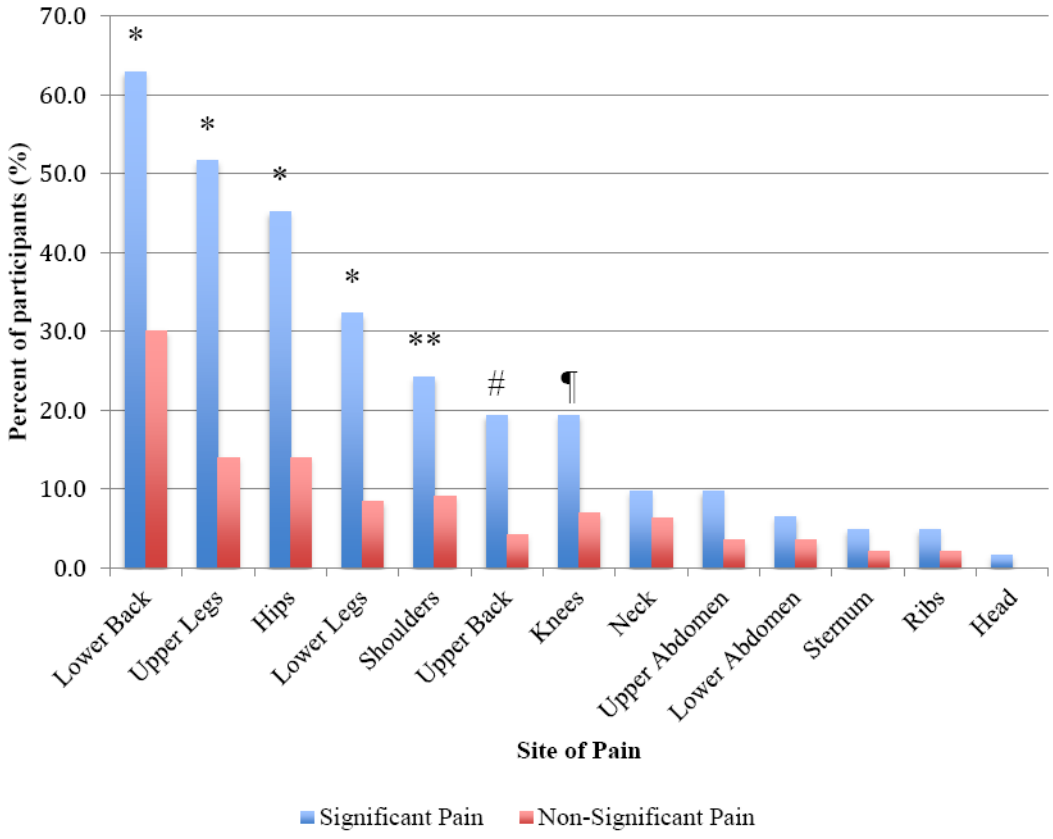

Figure 3.

Site of Pain at Day 8 of OBS† according to Pain Significance (per protocol definition)

* Fisher exact test, p <0.001

** Fisher exact test, p =0.007

Fisher exact test, p =0.001

¶ Fisher exact test, p=0.013

† Observation Stage

Table I

Clinical Characteristics of Patients in the OBS[a] (N=227).

Age (years)	
Median (range)	59 (22-90)
Gender	
Male	77 (33.9)
Female	150 (66.1)
Primary site	
Breast	99 (43.6)
Lung	30 (13.2)
Lymphoma	27 (11.9)
Genitourinary	20 (8.8)
Colorectal	16 (7.0)
Other Malignancies	15 (6.6)
Other Gastrointestinal	15 (6.6)
Head & Neck	5 (2.2)
Stage (N=214)	
Local	100 (46.7)
Metastatic	64 (29.9)
Locally-advanced	50 (23.4)
Taxane administration	71 (31.3)
Baseline back/leg pain (N=225)	
Any Site	115 (51.1)
Lower Back	61 (27.1)
Hips	30 (13.3)
Upper Legs	23 (10.2)
Knees	22 (9.8)
Lower Legs	21 (9.3)
Shoulders	18 (8.0)
Upper Back	11 (4.9)
Ribs	8 (3.6)
Neck	5 (2.2)
Upper Abdominal	4 (1.8)
Lower Abdominal	4 (1.8)
Head	1 (0.4)
Baseline Analgesic Use (N=214)[b]	
Non-NSAID	55 (25.7)
NSAID	22 (10.3)

[a] Observation Stage

[b] 8/214 (3.7%) of patients used both NSAID and Non-NSAID at baseline

Table II

Bony Pain Characteristics during OBS[f]

	Significant Pain Subset *mean (SD)* [a]	No Significant Pain Subset *mean (SD)* [b]	P value [c]
FACTBP QOL Score			
Day 1	51.7 (10.5)	52.8 (9.9)	NS [e]
Day 8	33.9 (14.6)	53.0 (8.8)	<0.001
Painful Site Number			
Day 1	1.1 (1.3)	0.8 (1.1)	NS [e]
Day 8	2.9 (1.9)	1.0 (1.3)	<0.001
Worst Back/Leg Pain Intensity [d]			
Day 1	1.8 (2.3)	1.6 (2.5)	NS [e]
Day 8	7.6 (1.7)	1.8 (2.2)	<0.001
Average Back/Leg Pain Intensity [d]			
Day 1	1.5 (2.1)	1.0 (1.8)	NS [e]
Day 8	5.1 (2.2)	1.3 (1.8)	<0.001
Sum of Worst and Average Back/Leg Pain			
Day 1	3.3 (4.1)	2.6 (4.1)	NS [e]
Day 8	12.6 (3.5)	3.0 (3.9)	<0.001

[a] Sample size of SP subset ranged between 62-65 due to missing data

[b] Sample size of non-SP subset ranged between 143-148 due to missing data

[c] Two-sample t-test at each day comparing SP and non-SP subsets

[d] Likert scale 1-10 (Brief Pain Inventory)

[e] Non-significant ($p > 0.05$)

[f] Observation Stage

Table III

Clinical characteristics of patients in the TRT[c].

	Loratadine arm (n=22) No. (%)	Placebo arm (n=24) No. (%)
Age		
Median (range)	55 (36-81)	55 (31-89)
Gender		
Male	8 (36.4)	3 (12.5)
Primary site		
Breast	12 (54.6)	16 (66.7)
Lung	3 (13.6)	1 (4.2)
Other Gastrointestinal	3 (13.6)	2 (8.3)
Other Malignancies	3 (13.6)	4 (16.7)
Colorectal	1 (4.6)	2 (8.3)
Taxane administration	11 (50)	11 (45.6)
NSAID use		
Day 1 [a, d]	4 (18.2)	2 (8.3)
Day 8 [b, e]	10 (45.5)	4 (16.7)
Non-NSAID use		
Day 1 [a, d]	5 (22.7)	6 (25)
Day 8 [b, e]	9 (40.9)	8 (33.3)

[a]NSAID and non-NSAID use unknown at day 1 in 1 (4.5%) and 3 (12.5%) of participants in the loratadine and placebo arms, respectively.

[b]NSAID and non-NSAID use unknown at day 8 in 2 (9.1%) and 3 (12.5%) of participants in the loratadine and placebo arms, respectively.

[c]Treatment Stage

[d]On Day 1, 0 and 1 patients used both NSAID and Non-NSAID in the loratadine and placebo arms, respectively.

[e]On Day 8, 3 and 1 patients used both NSAID and non-NSAID in the loratadine and placebo arms, respectively.