

Efficacy and safety analysis of once per cycle pegfilgrastim and daily lenograstim in patients with breast cancer receiving adjuvant myelosuppressive chemotherapy FEC 100: a pilot study

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Background: Neutropenia is a common toxicity in patients receiving myelosuppressive chemotherapy. In this prospective pilot study, we compared the efficacy and safety profiles of pegfilgrastim administered subcutaneously once per cycle and lenograstim administered subcutaneously daily six times per cycle, for primary neutropenia prophylaxis in women with breast cancer receiving adjuvant anthracycline-based chemotherapy.

Materials and methods: Twenty women were enrolled. All patients received epirubicin 100 mg/m² with 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m² on day 1 and every 21 days thereafter, according to the FEC 100 chemotherapy regimen. Eight patients received a single dose of pegfilgrastim on day 2, while 12 patients were treated with daily administration of lenograstim from days five to ten. Absolute neutrophil count and duration of grade 3–4 neutropenia were monitored using seriated blood samples. The incidence of bone pain was evaluated using the visual analog scale (VAS).

Results: The incidence of grade 3–4 neutropenia was 75% in patients who received pegfilgrastim, and 25% in patients who received lenograstim. One case of febrile neutropenia was shown in pegfilgrastim patients. The mean duration of grade 3–4 neutropenia was 2 days in pegfilgrastim group versus 1.4 days in the lenograstim group. Bone pain was present in 37.5% of pegfilgrastim patients versus 58.3% of lenograstim patients. The mean duration of bone pain in the pegfilgrastim group was 4 days versus 6 days in the lenograstim group.

Conclusion: In our experience, a single injection of pegfilgrastim was less effective for controlling neutropenia than six daily injections of lenograstim. The safety profiles of pegfilgrastim and lenograstim were similar with a lower incidence of bone pain in patients treated with pegfilgrastim.

Keywords: lenograstim, pegfilgrastim, neutropenia, bone pain, breast cancer, adjuvant anthracycline-based chemotherapy

Introduction

Neutropenia is a frequent and serious complication in patients treated with myelosuppressive chemotherapy. The grade and primarily the duration of neutropenia determine the risk of infection which results in the need to reduce the dose and to delay treatment, compromising antineoplastic treatment efficacy and the patient's prognosis.^{1–3} Moreover, febrile neutropenia (FN), despite the progress of antibiotic therapy, is still considered a medical emergency associated with significant morbidity, mortality, and high related costs.⁴ In patients receiving chemotherapy, the use of primary prophylaxis

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with granulocyte-colony stimulating factor (G-CSF) reduces the duration, severity, and incidence of neutropenia because these agents are able to regulate the production and release of neutrophils from the bone marrow.^{5,6} The indications for the use of primary prophylaxis with G-CSF depend on the risk of FN which is related to the aggressiveness and spread of the tumor, the type of chemotherapeutic regimen used, and the characteristics of the patients. Several randomized clinical trials have demonstrated a significant reduction in the risk of FN with prophylactic use of G-CSF in patients subjected to conventional chemotherapy.^{2,7-12} There are three forms of recombinant G-CSF: filgrastim, lenograstim, and pegfilgrastim.^{13,14}

Filgrastim is a recombinant methionyl non-glycosylated form of human G-CSF produced in *Escherichia coli*, whereas lenograstim is derived from Chinese hamster ovary (CHO) cells and glycosylated. Both require a daily administration to maintain their therapeutic effects because of their short circulating half-life (~3.5 hours). Therefore, a sustained duration form of filgrastim, pegfilgrastim, was developed.

The elimination of filgrastim and lenograstim occurs through renal excretion and by specific neutrophil regulatory mechanisms.^{15,16} Pegfilgrastim, due to PEGylation, has a reduced renal clearance and a long plasma half-life (~33 hours); therefore, this characteristic extends its pharmacological effect.

Moreover, pegfilgrastim acts on hematopoietic cells by binding to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation thus allowing a single administration of the drug per chemotherapeutic cycle.^{17,18} Several clinical trials involving patients with breast cancer undergoing chemotherapy have compared the efficacy of pegfilgrastim with filgrastim.^{11,18-20} These studies have shown that the incidence of neutropenia, both mild and severe (G3-G4), is not different between filgrastim and pegfilgrastim and consequently the efficacy of the two drugs is similar.

The most frequent side effect of G-CSF is bone pain, mainly due to the increase in mass of bone marrow and to the release of pro-inflammatory cytokines. Its incidence varies from 15% to 39% of treated patients.^{2,21} Some studies have compared the incidence of bone pain between PEGylated and non-PEGylated formulations of G-CSF. These clinical trials have shown, especially in breast cancer patients, that there is no statistically significant difference in the incidence of bone pain between filgrastim and pegfilgrastim.^{11,18,22} However, some of these studies have demonstrated that the incidence of bone pain varies between the first and the last cycle of chemotherapy.

All the above cited studies enrolled patients with breast cancer undergoing combination chemotherapy with anthracyclines and taxanes. To our knowledge, no trial has ever compared PEGylated and not-PEGylated formulations of G-CSF in terms of efficacy and toxicity in primary prophylaxis in patients receiving epirubicin 100 mg/m² with 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m² on day 1 and every 21 days thereafter (FEC 100).

Patients and methods

Twenty female patients (mean age 54 years) were enrolled following the inclusion and exclusion criteria listed in Table 1. All patients were evaluated in terms of treatment efficacy and toxicity. All patients gave signed consent to participate in the study and for the treatment of personal data. Twelve patients received primary prophylaxis with lenograstim and eight patients with pegfilgrastim. Patient characteristics are listed in Table 2. The measurement of clinical pain intensity was made using the visual analog scale (VAS).

Study design

This study investigated whether a single dose per cycle of pegfilgrastim is as safe and effective as multiple doses per cycle of lenograstim, in patients receiving their first cycle of adjuvant chemotherapy for breast cancer according to the FEC 100 regimen (epirubicin 100 mg/m² with 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m² on day 1 and every 21 days thereafter). Patients were assigned to one of two G-CSF administrations: a single subcutaneous injection containing a fixed dose of 6 mg pegfilgrastim on day 2 or six daily subcutaneous injections of lenograstim (263 µg) from day 5 to day 10, after administration of chemotherapy.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age > 18 years	Previous chemotherapy or radiotherapy treatment
ECOG performance status = 0	Metastatic disease
Absolute neutrophil count $\geq 1.5 \times 10^9/L$; platelet count $\geq 100 \times 10^9/L$	Bilirubin > upper limit of normal; or aspartate transaminase and/or alanine transaminase > 1.5× upper limit of normal and alkaline phosphatase > 2.5× upper limit of normal
Serum creatinine < 1.5× upper limit of normal	Heart failure with ejection fraction < 50%
High-risk stage II or stage III breast cancer	
High-risk stage I breast cancer	

Abbreviation: ECOG, The Eastern Cooperative Oncology Group.

Table 2 Demographic and medical characteristics of patients

	Lenograstim 12 patients	Pegfilgrastim 8 patients
Age (years)		
<65	10	7
>65	2	1
Mean	53	53
Range	37–71	42–66
Baseline ANC ($\times 10^9/L$)		
Mean	3,945	3,401
Minimum	2,490	2,360
Maximum	5,550	5,100
Clinical staging		
I	3	3
II	9	4
III	0	1

Abbreviation: ANC, absolute neutrophil count.

Seriated blood samples for determination of complete blood count with differential were performed on days 1, 8, 10, and 12, continuing daily until a rise of absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$ after the expected nadir. The patients' oral temperature was recorded daily and all patients were monitored for occurrence of adverse events during the study.

Objectives

The primary endpoint was to compare the incidence and duration of G3–G4 neutropenia (defined as ANC $< 0.5 \times 10^9/L$)

in the two groups of treatment during the first cycle of chemotherapy. Secondary endpoints were to assess the incidence of FN, hospitalization rate and the incidence, duration, and intensity of bone pain between the two treatment groups.

Results

In those patients treated with lenograstim, the overall incidence of neutropenia was 41.6% and severe neutropenia (G3–G4) occurred in 25% (8.3% neutropenia G3 and 16.7% neutropenia G4) of patients. The mean duration of severe neutropenia (G3–G4) was 1.4 days. No patient experienced FN, defined as ANC $< 0.5 \times 10^9/L$ and an oral temperature $\geq 38.2^\circ C$.

In those patients treated with pegfilgrastim we detected an overall incidence of severe neutropenia of 75% (12.5% neutropenia G3 and 62.5% neutropenia G4), while its mean duration was 2 days. One patient showed FN, which was treated with the administration of oral antibiotics. Hospitalization of patients or use of intravenous antibiotic therapy was not necessary in any cases (Figure 1).

In regards to the emergence of bone pain as the most common side effect, in patients treated with lenograstim we found an incidence of 58.3%, specifically VAS 3–4 in 16.7% of patients and VAS 7–8 in 41.7% of patients. The average duration of bone pain was 6 days.

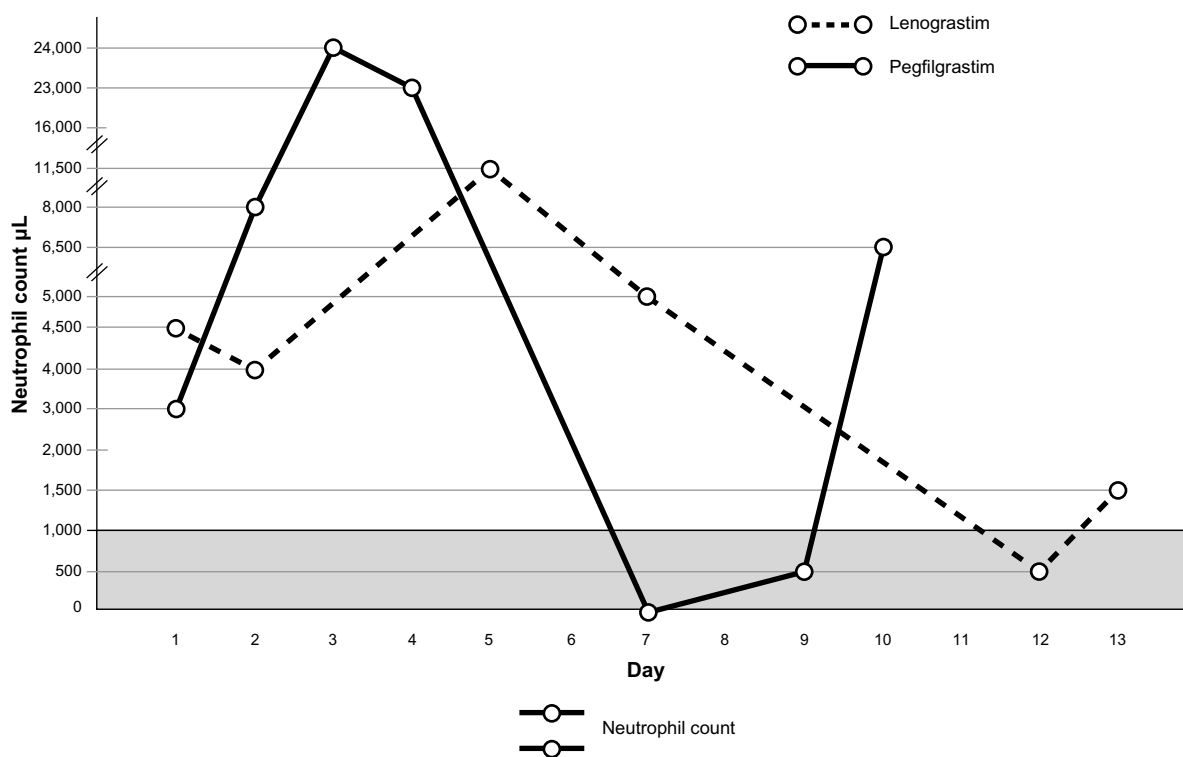


Figure 1 Neutrophil count in pegfilgrastim and lenograstim groups after first cycle of chemotherapy.

In patients treated with pegfilgrastim, bone pain was present in 37.5%. The average duration of bone pain was 4 days (Figure 2).

A summary of our data regarding neutropenia and bone pain in the lenograstim group and pegfilgrastim group is listed in Table 3.

Discussion

In patients receiving chemotherapy, the use of G-CSF for primary prophylaxis reduces the duration and severity of neutropenia and its related complications.^{5,6}

Currently, we have two types of granulocyte colony-stimulating factors: G-CSF in non-PEGylated formulations (lenograstim, filgrastim) and G-CSF in a PEGylated formulation (pegfilgrastim).

Our study compared the efficacy and side effects of lenograstim and pegfilgrastim, administered as primary prophylaxis in patients with breast cancer subjected to adjuvant chemotherapy according to the FEC 100 regimen.

The results showed that among patients treated with pegfilgrastim there was an incidence of severe neutropenia (G4) of 62.5% with a median duration of neutropenia of 2 days versus an incidence of 16.7% with an average duration of 1.4 days in the group treated with lenograstim. However, this difference did not result in an increase of the hospitalization rate of patients and in the pegfilgrastim group only one patient developed an episode of FN.

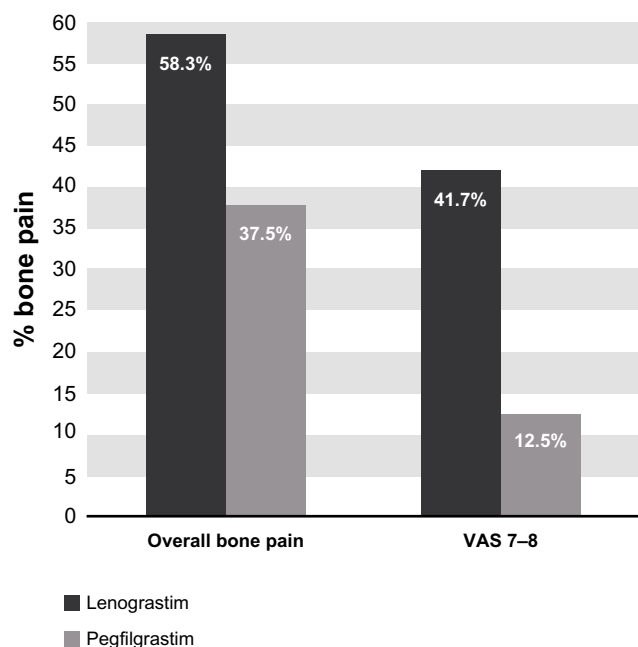


Figure 2 Incidence of bone pain in lenograstim and pegfilgrastim groups. **Abbreviation:** VAS, visual analog scale.

Table 3 Incidence of neutropenia and bone pain in lenograstim group and pegfilgrastim group

	Lenograstim Number of patients (%)	Pegfilgrastim Number of patients (%)
Neutropenia of any grade	5 (41.6%)	6 (75%)
Neutropenia G3	1 (8.3%)	1 (12.5%)
Neutropenia G4	2 (16.7%)	5 (62.5%)
Mean duration of neutropenia (days)	1.4	2
Febrile neutropenia	0	1
Overall bone pain	7 (58.3%)	3 (37.5%)
Bone pain VAS 7-8	5 (41.7%)	1 (12.5%)
Mean duration of pain (days)	6	4

Abbreviation: VAS, visual analog scale.

In the studies by Holmes et al^{18,20} and Green et al,¹¹ the incidence of severe neutropenia G4 in patients receiving primary prophylaxis with pegfilgrastim during the first cycle of chemotherapy was between 74% and 84%, with an average duration between 1.3 and 1.8 days. These results are essentially the same as reported in our study. The lower incidence of neutropenia G4 (62.5%) in our study can be explained by the different chemotherapy scheme used: generally, FEC 100 presents a lower incidence of neutropenia than a taxane/anthracycline combination such as doxorubicin and docetaxel, which was used by Holmes et al^{18,20} and Green et al¹¹ in the above mentioned studies.

Regarding the non-PEGylated G-CSF, Holmes et al^{18,20} and Green et al¹¹ found the incidence of severe neutropenia (G4) ranging between 76% and 83%, with an average duration between 1.6 and 1.8 days. However, in our study, the incidence of neutropenia G4 in patients treated with lenograstim was only 16.7% (mean duration 1.4 days), which is substantially lower compared to the data provided by Holmes et al^{18,20} and Green et al.¹¹ As discussed above, this discrepancy may be caused by the different chemotherapy schemes used (FEC 100 versus taxane/anthracycline). It is noteworthy that in the works by Holmes et al^{18,20} and Green et al,¹¹ an average number of eleven doses of filgrastim were administered, whereas in our study only six doses of lenograstim were administered. To date, there are no studies in literature comparing the efficacy of lenograstim versus pegfilgrastim with triplet chemotherapy FEC 100. In clinical trials using the adjuvant FEC 100 scheme in breast tumors, a steady supply of growth factors as primary prophylaxis was never provided, and therefore it is not possible to know exactly the efficacy of growth factors to prevent neutropenia in this setting. In some cases, G-CSF was administered as secondary prophylaxis or in other cases its use was banned during the course of the study.^{23,24}

Regarding bone pain, in the lenograstim group there was a greater incidence of this side effect compared to pegfilgrastim group (58.3% versus 37.5%, respectively), with a longer duration (6 versus 4 days, respectively); this difference was more evident when considering severe pain with VAS 7–8 (lenograstim: 41.7% versus pegfilgrastim: 12.5%), which, however, was well controlled in all cases with non-steroidal anti-inflammatory drugs.

Some studies have shown that the incidence of bone pain was comparable between the G-CSF and PEGylated G-CSF, with an incidence around 30%–40% for both growth factors.^{11,18}

More precisely, in the study by Green et al, the incidence of bone pain was 42% and 37% with filgrastim and pegfilgrastim, respectively, similar to our data, with a tendency toward a higher incidence in the filgrastim group.

In the study by Holmes et al,^{18,20} the incidence of bone pain was lower (25% in the pegfilgrastim group versus 26% in the filgrastim group) and comparable between the two growth factors.

However, in the two above mentioned works, the assessment of bone pain was not among the main endpoints of the study; thus, it is not possible to give a concrete explanation for the differences in the incidence of bone pain.

In contrast, a study by Kubista et al²² investigated as a primary end point the assessment of bone pain in patients who were treated with the two growth factors with detailed data collection for each cycle of chemotherapy. Kubista et al,²² specifically analyzed the incidence of bone pain for each chemotherapy cycle, highlighting how this effect tends to decline from the first cycle of treatment (filgrastim 34.2% versus 29.1% pegfilgrastim) to the last cycle (16.9% in both groups) for both growth factors and how in the filgrastim group bone pain was mainly present in the first few cycles but eventually overlapped with the pegfilgrastim group in the last few cycles. The study by Kubista et al,²² compared filgrastim versus pegfilgrastim usage at the same standard doses as used in our study. The results showed an incidence of bone pain of 42.8% in the filgrastim group versus 36.7% in the pegfilgrastim group, with a non-statistically significant trend towards an increased incidence in the filgrastim group. In this respect, the results of this study coincide with ours.

In contrast to the study by Kubista et al,²² in our study we evaluated bone pain only in the first cycle of chemotherapy. However, similarly to the aforementioned study, we found a higher incidence of bone pain in the non-PEGylated G-CSF lenograstim group (58.3%) compared to the PEGylated G-CSF pegfilgrastim group (37.5%). In our experience,

the incidence of bone pain with non-PEGylated G-CSF (58.3%) is slightly greater than that shown in other studies, while the incidence of bone pain in the pegfilgrastim group is comparable.

In conclusion, in our experience, although this study was carried out on a small sample of patients, six doses of lenograstim were sufficient to reduce the risk of neutropenia in primary prophylaxis with chemotherapy FEC 100 and we found no necessity for a greater number of injections which is suggested by some guidelines.^{25–27} Furthermore, we found that a single injection of pegfilgrastim, which has a higher cost, was less effective in controlling neutropenia than six daily administrations of lenograstim.

However, in other studies it was demonstrated that in breast cancer patients treated with anthracycline-based (without taxanes) adjuvant chemotherapy even a smaller number of doses of non-PEGylated G-CSF is sufficient to reduce the risk of neutropenia.²⁸

Other studies investigating chemotherapy in other tumors besides breast cancer (including lung, ovarian, colorectal, and lymphoma) demonstrated that five doses of non-PEGylated G-CSF were effective in controlling the risk of neutropenia.^{29–31}

With regard to the timing of administration of G-CSF, it should start 4–6 days before nadir, as was done in our study.³²

For bone pain, our study seems to confirm literature data; particularly that there is a trend towards an increased incidence with lenograstim, but essentially there is no difference in clinical relevance when comparison to pegfilgrastim.

Finally, we deem that further studies are required to determine the most efficient G-CSF and the most appropriate administration scheme, also in terms of cost/benefit, when used along with the FEC 100 regimen, considering that this chemotherapy protocol has been increasingly spreading in clinical practice and it is accompanied by a high risk of FN.

Disclosure

The authors report no conflicts of interest in this work.

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