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Therapeutic Administration of Pegfilgrastim Instead of Prophylactic Use

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Abstract. *Objectives: Pegfilgrastim is a new growth factor which can be administered subcutaneously once (versus multiple doses for days) on the day neutropenia occurs after chemotherapy. Our aims were to determine: a) the percentage of patients who needed growth factor (pegfilgrastim) supportive treatment, b) the duration of neutropenia-leukopenia after pegfilgrastim administration, and c) the safety in using pegfilgrastim as a treatment and not as a prophylactic agent. Materials and Methods: Ninety-eight patients were evaluated. All patients were scheduled to undergo chemotherapy treatment, which was either first- or second-line, and some patients had previously received granulocyte colony-stimulating growth factor (G-CSF): filgrastim on a daily basis. Twenty-five/98 patients required G-CSF support and were treated with pegfilgrastim 6 mg; the first 12 patients were admitted to hospital and remained until recovery from grade 3-4 neutropenia; the other 13 patients were treated on an out-patient basis or at home. Pegfilgrastim was administered when neutropenia appeared (days 6-8 following chemotherapy treatment). Results: Therapeutic administration of pegfilgrastim on the day serious neutropenia occurred was needed by 25/98 patients (25.51%). White blood cell recovery for both grade 3-4 neutropenia was observed within 1-3 days in 75% of the patients treated with pegfilgrastim and in the remaining 25%, within 5 days. Conclusion: Pegfilgrastim, an active hemopoietic growth factor with effective slow-absorption properties, can be used safely, not necessarily as a prophylactic agent but on an out-patient basis as a therapy for serious neutropenia.*

Myelotoxicity is a common adverse reaction to chemotherapy as well as a cytotoxic dose-limiting factor. The great majority of anticancer agents are moderately or highly myelotoxic (1-7). Bone marrow protection, particularly when cytotoxic drug combinations are used, is based on hemopoietic granulocyte colony-stimulating growth factors (G-CSF), which have been introduced into clinical practice in recent years (8-12). These growth factors have their place in clinical medicine and are administered when grade 3 and 4 neutropenia is present. This grade of myelotoxicity does not occur in all patients with the same disease/stage of disease, who are treated with the same combined chemotherapy. There is no neutropenia-predicting factor and the use of a hemopoietic growth factor prophylactically is guided by experience of how myelotoxic a certain chemotherapy combination is. Concern with regard to a high percentage of grade 3-4 neutropenia has naturally obliged clinicians to suggest the prophylactic use of growth factors. The percentages of G-CSF administrations in a number of studies, that is to say, the percentage of patients with neutropenia, varies from <10% to approximately 75% (13-21). In the latter cases, the toxicity of the treatment is considered unacceptable despite G-CSF support and the chemotherapy is modified. Dilemmas always exist in clinical medicine. Those who suggest the prophylactic use of G-CSF claim that patients are being protected from severe neutropenia and thus obviate hospitalization, antibiotics or other costly supportive treatment. The prophylactic use of G-CSF can be supported when a high number of patients, *i.e.* a percentage of >50%, avoid the consequences of grade 3-4 neutropenia and hospitalization.

Pegfilgrastim (Neulasta) is a bioengineered form of r-met Hu G-CSF, created by attaching a polyethylene glycol (PEG) molecule at the N-terminal methionine residue of the filgrastim protein. This pegylation reduces renal clearance, which results in a sustained duration of action by Neulasta as compared to filgrastrim.

Since all studies related to Neulasta are based on prophylactic use on day 2, we decided to perform a study in patients in whom neutropenia was expected to occur, and to administer this growth factor, not prophylactically but on the day the patients became neutropenic. Our objectives were to determine: a) the percentage of patients who needed G-CSF (pegfilgrastim) supportive treatment, b) the duration of neutropenia-leukopenia after G-CSF administration – or the duration in hours or days of white blood cell count recovery, and c) the safety in using pegfilgrastim as a treatment and not as a prophylactic agent in neutropenia, taking cost-effectiveness into account.

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Table I. *Pegfilgrastim-treated and non-treated patients.*

	Pegfilgrastim		
	Treated patients	Non-treated patients	
Malignant tumor	n (%)	n (%)	Total
Breast (advanced)	5 (33.3)	10 (66.67)	15
Breast (adjuvant)	1 (6.25)	15 (93.75)	16
NSCLC	3 (15.79)	16 (84.21)	19
SCLC	4 (36.36)	7 (63.64)	11
Head and neck	3 (42.86)	4 (57.14)	7
Pancreas	3 (27.27)	8 (72.73)	11
Gastric	3 (42.86)	4 (57.14)	7
Bladder	2 (33.33)	4 (66.67)	6
Ovary	1 (16.67)	5 (83.33)	6
Totals	25 (25.51)	73 (74.49)	98

Table II. *Chemotherapy administered to patients.*

	No. of patients	Cytotoxic combination	Cycle
Breast (adjuvant)	16	Epirubicin 77 mg/m^2 Paclitaxel 175 mg/m^2	3 wk
Breast (advanced)	15	Doxorubicin 60 mg/m^2 Paclitaxel 175 mg/m^2	3 wk
NSCLC	19	Carboplatin 6 AUC Paclitaxel 175 mg/m^2	3 wk
SCLC	11	Cisplatin 250 mg/m^2 Paclitaxel 60 mg/m^2	weekly
Head and neck	7	Cisplatin 100 mg/m^2 Paclitaxel 200 mg/m^2	3 wk
Pancreas	11	Gemcitabine 1 gr/m^2 1st & 8th day Irinotecan 300 mg/m^2 8th day	3 wk
Gastric	7	Carboplatin 6 AUC Paclitaxel 175 mg/m^2	3 wk
Bladder	6	Cisplatin 100 mg/m^2 Gemcitabine 1 g/m^2	3 wk
Ovary	6	Carboplatin 6 AUC Paclitaxel 175 mg/m^2	3 wk

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

Materials and Methods

Study design. This study had an observational character, by defining, during clinical practice, the number of patients that do need G-CSF support.

On the basis of pegfilgrastim treatment of neutropenia only when it occurs and not prophylactically, two consecutive study period groups were defined. The first study period group included a number of patients who presented with grade 3-4 neutropenia on the 6-8th day after chemotherapy and who were admitted to hospital a) for safety reasons and b) to check their blood count every 12 hours after pegfilgrastim injection and determine the length of time until recovery. Patients remained hospitalized until their neutrophil count was normal.

The second study period group, which chronologically followed the first, included patients who received pegfilgrastim on an out-patient basis or at home. These patients also had the G-CSF injection when grade 3-4 neutropenia occurred; they were instructed to closely communicate with the clinician in cases of febrile consequences and to repeat the blood test 2-3 days later. At the same time, patients undergoing the same chemotherapy (cytotoxic agents) according to malignancy were also followed-up by blood count examination on days 6-8 after chemotherapy. Having had the experience with the first group of patients with regard to safety and outcome, we decided on pegfilgrastim treatment on an out-patient basis or at home.

Neutropenia occurs following chemotherapy in several malignant tumors, so we included several malignancies with different chemotherapy combinations known to be myelotoxic.

Treatment. Twelve patients (first study period group), who were hospitalized when grade 3-4 neutropenia occurred, were given 6 mg pegfilgrastim on admission and remained until their neutrophil count recovered. Pegfilgrastim was injected subcutaneously on the day neutropenia appeared (days 6-8) after chemotherapy administration. In hospitalized patients, blood was taken every 12 hours after pegfilgrastim administration for blood count and for a time period of 3-5 days, until the white blood cell count returned to normal levels (4,000 /mm^3).

The second study period group did not have to be hospitalized if no febrile neutropenia occurred; these patients were given 6 mg pegfilgrastim once on the day grade 3-4 neutropenia appeared and their white blood cell count was tested every 2 days on an out-patient basis.

Patient evaluation and selection. Pretreatment evaluation included medical history and physical examination, full blood cell count, biochemical profile and all of the tests that patients require when they are to be treated with myelotoxic chemotherapy: histology, stage of disease (CT-scans), electrocardiogram. Enrolled patients were randomly included and had a variety of malignancies with advanced disease and also primary disease, who had adjuvant chemotherapy and were scheduled to receive myelotoxic chemotherapy with a combination of cytotoxic drugs. Patients undergoing first- or second-line chemotherapy, some of whom had had G-CSF previously, were included. In all the patients, chemotherapy was administered on day one and repeated on day 15, at the earliest. Full blood count, blood urea and serum creatinine tests were performed before chemotherapy administration and on day 6 after chemotherapy. White blood cell count grading was based on WHO criteria.

All patients gave their informed consent and the study was conducted with the approval of the Institution's Review Board.

Results

This study lasted for 5 months, during which 98 patients, 49 males, 49 females, >18 years old (median 55 years, range 32-75 years), were evaluated. Sixteen patients with breast cancer were treated with adjuvant chemotherapy. The remaining 82 patients had advanced disease. Chemotherapy treatment was based on the type of malignancy and it was the same for those patients who required G-CSF and those who did not. In Table

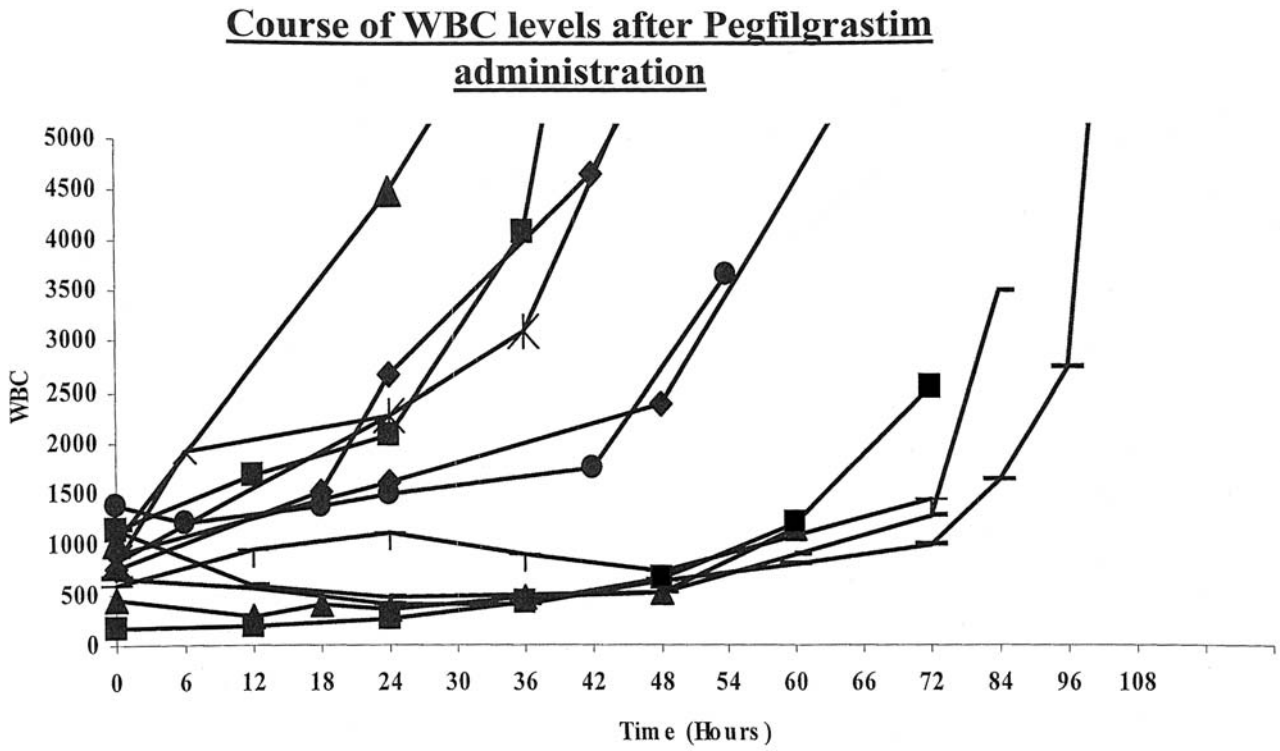

Figure 1. *White blood cell recovery in the first study period group patients.*

I, patients are classified according to the different malignant tumors and on the basis of pegfilgrastim treatment and non-treatment.

Chemotherapy. The type of chemotherapy for each tumor is shown in Table II.

Response to pegfilgrastim. Of the 98 patients, 25 (25.51%) presented with grade 3 and 4 neutropenia on the 6th-8th day after chemotherapy. Seventy-three patients, despite the same kind of chemotherapy related to the type of tumor, had either grade 1-2 myelotoxicity or no myelotoxicity (Table I).

The recovery of the white blood cell count for both grade 3-4 neutropenia was seen within 72 hours (3 days) in 75% of the treated patients and in the remaining 25% within 5 days (Figure 1). Only 2 patients presented with febrile neutropenia grade 4 and these were patients who had been heavily pretreated with chemotherapy.

Discussion

Pegfilgrastim has already been proven to be an active growth factor, equally as effective as filgrastim (22). Apart from its effectiveness, existing trials have also clarified the pharmacokinetics of pegfilgrastim (23-25). With one subcutaneous injection and its slow absorption, the product remains in the bone marrow until mature white blood cells recover to a normal count.

By using pegfilgrastim prophylactically on day 2, one achieves less serious myelotoxicity and diminished febrile neutropenia, which consequently results in avoiding hospitalization and the use of antibiotics in a major percentage of patients – this is accepted. Also, undoubtedly one injection is much more comfortable for the patient than ≥5-7 daily injections. The present study clarifies unknown parameters: a) How long does it take for the patient to recover from grade 3 or 4 neutropenia after the administration of pegfilgrastim and b) how many of the patients treated with the same cytotoxic chemotherapy require growth factor supportive treatment? Having clarified these parameters, it is safe to suggest the administration of pegfilgrastim on the day grade 3 or 4 neutropenia occurs.

Seventy-five percent of patients with serious neutropenia recovered within 3 days (72 hours). The rest recovered within 5 days (Figure 1). The difference in recovery time is probably dependent on bone marrow cellularity, *i.e.* how heavily or not patients have been pretreated by chemotherapy and/or radiotherapy.

Of the 98 patients who underwent the same chemotherapy regimen per malignancy, a percentage that varied from 6.25% to 42.86% (mean 25.51%) was found to require pegfilgrastim

treatment. Twenty-five out of 98 patients needed G-CSF, which is to say that 73 patients did not require G-CSF prophylactically. With respect to cost-effectiveness, 12 (12.24%) were hospitalized, which might have resulted in increased cost, but for 13 (13.27%) patients hospitalization was not required, although they had the G-CSF treatment; for the remaining 74.49% of patients, there was a cost reduction since an expensive new hemopoietic growth factor was not administered.

In conclusion, on the basis of this study, we suggest that pegfilgrastim is active as a hemopoietic growth factor; it can be used safely, not necessarily as a prophylactic agent, but on an out-patient basis as a therapy for serious neutropenia. The outcome of the present study contributes to the therapeutic value of pegfilgrastim. Its prophylactic use may be of importance in cases where neutropenia can be predicted.

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