Safety and efficacy of pegfilgrastim in children with cancer receiving myelosuppressive chemotherapy

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The myelotoxicity of most chemotherapeutic regimens used to treat children and adolescents with cancer require the use of daily subcutaneous administration of hematological growth factors (mainly granulocyte colony-stimulating factor). Recently, pegfilgrastim (Neulasta), a product with a long half-life, resulting in once-per-cycle dosage, was introduced to prevent neutropenia in adults, and provided safety and efficacy similar to that provided by daily injection of filgrastim. To evaluate retrospectively the use of pegfilgrastim in children with cancer, we conducted a single-center retrospective study evaluating the use of pegfilgrastim in patients over 40 kg, who received chemotherapy for cancer from September 2003 to December 2005. A single subcutaneous injection of pegfilgrastim 100 μg/kg (maximum dose 6 mg) per chemotherapy cycle in children receiving myelosuppressive chemotherapy was given. One hundred and twenty-six administrations of pegfilgrastim were analyzed in 28 pediatric patients treated for cancer (11 girls, 17 boys) with a median age of 14.5 years (range 12–18 years) and median weight of 50.5 kg (range 40–82 kg). Patients received a median dose of pegfilgrastim of 100 μg/kg (range 73–117). The median total number of injections per patient was 4 (range 1–14). The incidence of grade 4 neutropenia by cycle was 48%, the mean duration of neutropenia was 3 days (range 1–13 days). The median values of absolute neutrophil count nadir was 0.425×10^9/l (range $0–9.9 \times 10^9$). Febrile neutropenia occurred in 18 of the 126 patients on pegfilgrastim use (14%) with full recovery in all patients. The median total duration of intravenous antibiotic therapy was 5 days (range 2–14 days). Bone pain (four) and headaches (two) were the most frequent adverse events reported. No correlation was found between the administered dose of Neulasta and hematological data. In conclusion, the use of pegfilgrastim was safe and well tolerated in children with cancer treated with myelosuppressive chemotherapy. Safety and efficacy of pegfilgrastim must be compared with filgrastim and evaluated in younger children with lower body weight. *Anti-Cancer Drugs* 18:277–281 © 2007 Lippincott Williams & Wilkins.

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Introduction

Chemotherapy-induced neutropenia is the primary dose-limiting toxicity in children with cancer treated with myelosuppressive chemotherapy [1]. It has substantial cost with clinical, economic and quality-of-life consequences. Therefore, managing chemotherapy-induced neutropenia is a major concern in the treatment of children with cancer [2].

The development of granulocyte colony-stimulating factors (G-CSFs), such as filgrastim, more than a decade ago has markedly changed the course of treatment in many children with cancer, who, previously had had to accept potentially life-threatening infection related to their treatment, in the absence of effective prophylactic support [3,4]. Thus, in their meta-analysis, Sung *et al.* [5] recently reported that prophylactic use of hematopoietic colony-stimulating factors was associated with a 20% reduction in febrile neutropenia and shorter duration of hospitalization among children. They, however, also demonstrated that prophylactic use of hematopoietic colony-stimulating factors did not reduce infection-related mortality.

A significant advance in the field of neutrophil growth factors has occurred with the commercial availability of pegfilgrastim (Neulasta; Amgen, Thousand Oaks, California, USA), a new generation, pegylated filgrastim molecule with a sustained duration of action [6,7]. Pegfilgrastim is composed of the protein filgrastim to which a 20-kDa polyethylene glycol is covalently bound at the N-terminal residue. Consequently, its renal clearance by glomerular filtration is minimized, making neutrophil-mediated clearance the predominant route of elimination

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resulting in an increased plasma half-life compared with filgrastim [8].

Pegfilgrastim significantly reduces scheduling protocols to a single injection per chemotherapy cycle while maintaining therapeutic efficiency. Other interesting effects have also emerged, such as the self-regulating pharmacokinetics of pegfilgrastim. Indeed, pegfilgrastim clearance is regulated predominantly by neutrophils and their precursors, thus when the neutrophil count increases the drug is progressively cleared, creating a 'self-regulating' mechanism.

In adults, clinical data from two randomized trials demonstrate equivalence of pegfilgrastim and filgrastim in duration of severe neutropenia and recovery from absolute neutrophil count nadir after myelosuppressive chemotherapy [9–11].

Sung *et al.* [5] recently included in their meta-analysis 16 studies assessed G-CSFs for primary prophylaxis in children with cancer, confirming their interest. Nevertheless, data in pediatrics are rare as only two studies concerning the use of pegfilgrastim among children with cancer have been reported [1,12].

We examined the safety and efficacy of pegfilgrastim in children with cancer receiving myelosuppressive chemotherapy.

Patients and methods

Children with cancer treated from September 2003 to December 2005 in the Department of Pediatric Oncology of the Children Hospital of 'la Timone' in Marseille, treated with myelotoxic chemotherapy for solid tumors and who had a weight over 40 kg were offered prophylaxis by pegfilgrastim instead of filgrastim. Children who received pegfilgastrim were included in this single-center retrospective study evaluating the use of pegfilgrastim (Neulasta). A single subcutaneous injection of pegfilgrastim was administered at the dose of 100 μg/kg 48–72 h after chemotherapy. As among adults, the maximum dose received was 6 mg. Informed consent was obtained from parents and children when possible. Blood counts were performed twice weekly as routine monitoring of hematological toxicity. No additional blood counts were performed for the study. No prophylactic antibiotic or antifungal therapy was given.

Data were retrospectively collected from patient charts. Data included patient characteristics, type of chemotherapy administrated, the first peak in absolute neutrophilic count (ANC) (most elevated number of ANC before the nadir), the ANC nadir, the second peak in ANC (most elevated value of ANC after the nadir and before the next chemotherapy), together with the presence of grade 4 neutropenia, length of grade 4 neutropenia, length of antibiotic treatment, length of hospital stay, type of infection and adverse events. World Health Organization criteria for neutropenia grade 4 (0.5×10^9/l) were used. Safety was assessed by recording adverse events such as musculoskeletal pain (World Health Organization criteria).

One hundred and twenty-six cases of pegfilgrastim use in 28 pediatric patients with cancer were analyzed. Baseline demographics and disease status of the patients are given in Table 1.

Data collection and statistical analysis were performed using SPSS. Correlations between the received dose of pegfilgrastim and the first peak in ANC, the ANC nadir, the second peak in ANC, length of grade 4 neutropenia, length of antibiotic treatment and length of hospital stay were calculated using a Pearson test. Correlation values under 0.2 were considered as not clinically significant.

Results

Pegfilgrastim administration

A total of 126 administrations of pegfilgrastim were administered in 28 patients at the median dose of 100 μg/kg per chemotherapy cycle (range 73–117 μg/kg). The median total number of injections administered per patient was 4 (range 1–14 injections). Pegfilgrastim was administered 48 h (70% of cases) to 72 h (30% of cases) after chemotherapy.

Absolute neutrophil count profiles

After administration of pegfilgrastim, the median values and extremes of first increase in ANC, ANC nadir

Table 1 Patient characteristics

Characteristics	Single-dose pegfilgrastim ($n=126$)
Age (years)	
Median	14.5
Range	12–18
Sex	
Boys	17
Girls	11
Weight (kg)	
Median	50.5
Range	40–82
Injections of pegfilgrastim	
Median	4
Range	1–14
Disease	28
Osteosarcoma	9
Ewing tumor	7
Rhabdomyosarcoma	2
Nephroblastoma	3
Synovialosarcoma	1
Medulloblastoma	1
SETTLE syndrome	1
Yolk sac tumor	1
Cerebral MGT	1
Chondrosarcoma	1
Atypical teratoid rhabdoid tumor	1

SETTLE, spindle epithelial tumor with thymus-like differentiation; MGT, malignant germinal tumor.

and second increase in ANC were 4.6×10^9/l (range $1.17–63.54 \times 10^9$/l), 0.425×10^9/l (range $0–9.9 \times 10^9$/l) and 4.99×10^9/l (range $0.2–62 \times 10^9$/l), respectively.

Neutropenia and infection

The incidence of grade 4 neutropenia was 48% (61 episodes of pegfilgrastim) in 21 children (82%). The mean duration of grade 4 neutropenia was 3 days (range 1–13 days).

Febrile neutropenia occurred in 18 of the 126 cases of pegfilgrastim use (14%) with no documented infections. The median total duration of intravenous antibiotic therapy was 5 days (range 2–14 days). All patients fully recovered after intravenous antibiotic therapy.

Overall, five courses (3.9%) of chemotherapy were delayed in four patients (9.4%). Among these delays only two were due to prolonged febrile neutropenia (Table 2).

Adverse effect

The most frequently reported adverse event was bone pain, developed in four of the 126 cases of pegfilgrastim administration (3%). Head pain resulted after two administrations in one patient and pain at the point of subcutaneous injection of pegfilgrastim in two cures. Bone pain was mild to moderate in severity and was successfully treated with acetaminophen.

Statistical analysis

No significant correlation between the dose/kg of pegfilgrastim and duration of grade 4 neutropenia, duration of febrile neutropenia, duration of antibiotherapy, first increase, nadir and second increase in ANC was found.

Discussion

Hematological toxicity associated with neutropenic complications is a major dose-limiting toxicity of cancer chemotherapy. The use of pegfilgastrim has been associated with recovery from ANC nadir after myelosuppressive chemotherapy and a reduced risk of febrile neutropenia in adults [9–11]. Only quite limited data, however, have been reported so far on the use of pegfilgrastim in pediatric oncology [1,12].

In this retrospective study, we report 126 cases of pegfilgrastim use in 28 pediatric cancer patients. It is of the highest interest that 96% of the chemotherapy cycles could be started on time. Only two chemotherapy courses were delayed because of neutropenia. Similarly, te Poele *et al.* [1] showed that neutropenia rarely caused a delay in the beginning of chemotherapy when pegfilgrastim was used. Instead, they noted that thrombopenia was the limiting factor in 25% of the courses. In our study, grade 4 thrombopenia occurred in 6% of the chemotherapy courses and thrombopenia induced a delay in chemotherapy in only one case. Additionally, thrombopenia was a limiting factor in only three cases. Thus, although our observations do not comfort their findings regarding the impact of thrombopenia and no data in the literature associate the use of pegfilgarstim and thrombopenia, it will be interesting in the future to investigate whether the use of pegfilgrastim allows neutropenia not to be the limiting factor any longer or if the use of pegfilgrastim may disturb platelet recovery. Indeed, similarly, Papaldo *et al.* [13] recently reported that G-CSF might worsen anemia in breast cancer patients treated with epirubicine and cyclophosphamide. The underlying mechanism may be that red cell progenitor compartment could be inhibited by high doses of G-CSF, which could cause the reduction of immature cell stages by the mobilization

Table 2 Occurrence of neutropenia and febrile neutropenia according to the chemotherapy course

Chemotherapy	Number of episodes	Neutropenia	%	Febrile neutropenia	%
VIDE	17	14	82	8	47
VAC	26	5	19	1	4
VAI	6	3	50	2	33
Etoposide–ifosfamide	20	11	55	2	10
Etoposide–carboplatine	10	6	60	1	10
Cyclophosphamide–adriamycine	3	1	33	0	0
CDDP–adriamycine	8	5	62	1	12
Docetaxel–5-FU	4	1	25	0	0
Docetaxel-gemcitabine	2	0	0	0	0
ICE	11	7	64	2	18
IVA	3	1	33	0	0
CEV	3	3	100	0	0
IVE	3	1	33	0	0
Topotecan-cyclophosphamide	5	1	20	0	0
Cyclophosphamide–carboplatine–adriamycine	2	0	0	0	0
Cyclophosphamide–carboplatine–etoposide	2	2	100	1	50
Paclitaxel–oxalipatine	1	0	0	0	0

VIDE, vincristine–ifosphamide–voxorubicin–etoposide; VAC, vincristine–actinomycin–D–cyclophophamide; VAI, vincristine–actinomycin–D–ifosphamide; ICE, ifosphamide–carboplatin–etoposide; IVA, ifosphamide–vincristine–actinomycine; CEV, carboplatin–epirubicine–vincristine; IVE, ifosphamide–vincristine–etoposide; CDDP, cisplatin; IFO, ifosfamide.

of these cells from the marrow to the blood, causing competition for a common stem cell.

In our experience, neutropenia occurred in 48% of the chemotherapy cycles. This is higher than the results of a pediatric study [1], which reported that neutropenia occurred in *22%* of the cases after administration of different kinds of chemotherapy courses. In a later study, the numbers of patients and cases of pegfilgrastim administration (32 injections) were much lower. Nevertheless, in our study, febrile neutropenia occurred in only 14% of the episodes with full recovery of all patients after intravenous antibiotic therapy. A randomized trial in children with Ewing sarcoma receiving either G-CSF or pegfilgrastim has shown a higher percentage (78%) of neutropenia but all patients received the highly hematotoxic chemotherapy cycle (vincristine, ifosphamide, doxorubicin, etoposide). This study also showed that the duration of severe neutropenia and the incidence and duration of febrile neutropenia after once-per-cycle pegfilgrastim and daily filgrastim were comparable [12]. Sung *et al.* [5] found that prophylactic G-CSFs in children with cancer reduced the rate of febrile neutropenia by 20%, leading to similar results as those reported here and by te Poele *et al.* [1]. Nevertheless, additional studies are required to confirm if pegfilgrastim is as efficient as filgrastim in reducing neutropenia and neutropenia related morbidities.

The safety end point of this study was assessed in terms of occurrence of adverse events; most were attributable to complications associated with myelosuppressive chemotherapy. The most frequently reported pegfilgrastim-related adverse event was mild to moderate bone pain appearing in four of the 126 cases of pegfilgrastim use (3%). Interestingly, even in cases of very high neutrophil counts after the nadir, no bone pain was noted. Headaches following pegfilgrastim administrations were noted twice in one patient and pain at the site of subcutaneous injection of pegfilgrastim twice. Thus, even though recording of clinical pegfilgrastim-related adverse events was carefully performed, the retrospective setting may induce a bias with under-reporting of adverse events. This may also be the case for the two previously published pediatric studies, which both report very rare adverse events [1,12]. Indeed, in a pediatric study of the use of pegfilgrastim in patients with Ewing sarcoma, bone pain was noted in only one patient after one cycle (3%) [12]. Similarly, in the second pediatric study of pegfilgrastim in children, no adverse events were recorded [1]. Similarly, in adults, clinical adverse events attributed to pegfilgrastim were limited to bone pain. No apparent relationship was found between pegfilgrastim dose and patient frequency of bone pain [14]. A meta-analysis of five controlled trials indicates that the overall incidence of clinical adverse events ranged from 20 to 50% [15]. Furthermore, no statistically significant differences in incidence, severity or duration of bone pain were observed between patients receiving pegfilgrastim or filgrastim [16]. Thus, pegfilgrastim tolerance is good.

The administration of pegfilgrastim can lead to a peak in ANC either before or after the occurrence of ANC nadir. Thus, in 11% of our chemotherapy cycles (14 cases in seven patients), we observed a number of ANC above 30×10^9/l with a maximum leukocyte count of 63×10^9/l before occurrence of ANC nadir. We have also noticed twice a number of ANC above 30×10^9/l after ANC nadir and a maximum leukocyte count as high as 62×10^9/l.

No information regarding the potential long-term pathological consequences of such repeated nonphysiological stimulations are available. Nevertheless, as G-CSF may contribute to the genesis of secondary leukemia, for example, in patient acute myeloblastic leukemia or myelodysplasic syndrome especially in cases of chemotherapy containing etoposide [17], the intense repeated bone marrow stimulations induced by pegfilgrastim should be carefully evaluated in the long term. Furthermore, modifications of the schedule of administration of pegfilgrastim may be improved in children to avoid this peak in ANC: (1) pegfilgrastim dosage may be decreased and (2) the administration of pegfilgrastim may be delayed until day 5 after completion of the chemotherapy course. The occurrence of high ANC must be confirmed by additional studies before the need for a strategy to optimize pegfilgrastim administration can be decided.

Conclusion

In our experience, pegfilgrastim can be safely administered to patients with various kinds of cancer and receiving several kinds of chemotherapy courses. As only one injection per cycle of chemotherapy is required, pegfilgrastim may improve patient quality of life because it is less disruptive to patients and caregivers, and increase adherence because no doses are missed. Additional studies are required to determine the optimum dosing according to the age or weight of the patients and optimum timing of administration, and compare its efficacy when compared with nonpeggylated G-CSF.

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