Phase II, Randomized, Open-Label Study of Pegfilgrastim-Supported VDC/IE Chemotherapy in Pediatric Sarcoma Patients

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ABSTRACT

Purpose

This multicenter, randomized, open-label study evaluated the efficacy, safety, and pharmacokinetics of a single subcutaneous pegfilgrastim injection with daily subcutaneous filgrastim administration in pediatric patients receiving myelosuppressive chemotherapy for sarcoma.

Patients and Methods

Forty-four patients with previously untreated, biopsy-proven sarcoma stratified into three age groups (0-5, 6-11, and 12-21 years) were randomly assigned in a 6:1 randomization ratio to receive a single pegfilgrastim dose of 100 μ g/kg ($n = 38$) or daily filgrastim doses of 5 μ g/kg ($n = 6$) after chemotherapy (cycles 1 and 3: vincristine-doxorubicin-cyclophosphamide; cycles 2 and 4: ifosfamide-etoposide). The duration of grade 4 neutropenia, time to neutrophil recovery, incidence of febrile neutropenia, and adverse events were recorded.

Results

Pegfilgrastim and filgrastim were similar for all efficacy and safety end points, and their pharmacokinetic profiles were consistent with those in adults. Younger children experienced more protracted neutropenia and had higher median pegfilgrastim exposure than older children.

Conclusion

A single dose of pegfilgrastim at 100 μ g/kg administered once per chemotherapy cycle is comparable to daily injections of filgrastim at 5 μ g/kg for pediatric sarcoma patients receiving myelosuppressive chemotherapy.

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INTRODUCTION

Dose-intensive chemotherapy has become routine for the treatment of most pediatric sarcomas because chemotherapy dose-intensity correlates with tumor response and outcome.¹⁻³ Neutropenia is a common toxicity of these regimens.⁴⁻⁶ Both the depth of the neutrophil nadir and duration of severe neutropenia influence the development of infectious complications.^{7,8} Therefore, preventing or shortening the duration of neutropenia following chemotherapy may facilitate dose-intensity, improve safety, and control costs.

Filgrastim (r-metHu G-CSF) stimulates proliferation and maturation of neutrophil precursors^{9,10} and shortens the duration of neutropenia^{8,11,12} and its associated complications.^{8,12-15} Its use has become routine after chemotherapy for pediatric sarcomas^{5,6} and has permitted chemotherapy dose intensification via interval compression in pediatric sarcoma patients.¹⁶

A significant impediment to administering filgrastim after chemotherapy is its daily administration schedule, typically for approximately 10 days.¹⁷ In pediatric patients, filgrastim administration can be problematic. Even if parents learn to administer the injections themselves, doing so in young children often requires two caregivers and may result in psychological effects for parents and quality of life impairment of young cancer patients, although this has not been well studied.

Pegfilgrastim comprises filgrastim bound to a 20-kDa polyethylene glycol molecule. Pegylation decreases renal clearance and extends circulation half-life, resulting in sustained drug activity.¹⁸⁻²⁰ Pegfilgrastim clearance is predominantly mediated by neutrophils, so the drug concentration is sustained in the circulation during chemotherapy-induced neutropenia and rapidly eliminated on neutrophil recovery.^{21,22} In adults, a single dose of pegfilgrastim (either 100 μ g/kg or 6 mg) after chemotherapy has demonstrated safety and efficacy

Fig 1. CONSORT diagram. (*) One patient was withdrawn before study drug administration because of concerns about protocol-required blood draws after migration and infiltration of the patient's intravenous catheter. (†) Treatment completion was defined as completing all planned cycles of study drug.

similar to daily filgrastim^{17,23}; the recommended adult dosage is 6 mg administered subcutaneously once per chemotherapy cycle. A limited number of studies have evaluated pegfilgrastim dosing in pediatric patients.²⁴⁻²⁹ This phase II study was designed to evaluate the safety, clinical response, and pharmacokinetics of pegfilgrastim in pediatric patients with sarcoma receiving dose-intensive vincristine-doxorubicin-cyclophosphamide/ifosfamide-etoposide (VDC/IE) chemotherapy.

PATIENTS AND METHODS

Patient Population

This study was approved by the institutional review board of participating centers. All patients or their legal guardian gave written informed consent before study entry. Authors had access to study data for interpretation of study results. Patient eligibility criteria (Appendix Table A1, online only) included newly diagnosed sarcoma, age younger than 22 years, and no bone marrow involvement by tumor.

Study Design

This multicenter, open-label, randomized study was initiated in 2000 and was subsequently included as part of pegfilgrastim's postmarketing commitments. It evaluated the safety, clinical response, and pharmacokinetics of a single pegfilgrastim injection in a 6:1 randomization ratio with daily filgrastim injections until neutrophil recovery in previously untreated patients with biopsy-proven sarcoma receiving four cycles of chemotherapy. The CONSORT diagram and study design are shown in Figure 1 and Figure 2, respectively. Amgen (Thousand Oaks, CA) supplied pegfilgrastim and filgrastim. Pegfilgrastim dosage of 100 $\mu\text{g/kg}$ was chosen on the basis of efficacy and safety data in adults.^{22,30,31} Because of the wide range of ages and body weights in the pediatric population, weight-based dosing (100 $\mu\text{g/kg}$) for pegfilgrastim was used. Safety of the weight-based dosage was evaluated in the first three patients enrolled. After documenting an acceptable safety profile in these patients, additional patients were randomly assigned (six to pegfilgrastim, one

to filgrastim), and treatment arms were divided into three age strata (0-5, 6-11, and 12-21 years).

Patients randomly assigned to the filgrastim group received 5 $\mu\text{g/kg}$ filgrastim subcutaneously daily beginning approximately 24 hours after chemotherapy completion in week 1 (generally, day 4 in cycles 1 and 3 and day 6 in cycles 2 and 4) and continuing either until a postnadir absolute neutrophil

Fig 2. Study schema. Chemotherapy: Vincristine-doxorubicin-cyclophosphamide (VDC) cycles 1 and 3 (vincristine [V] at 2.0 mg/m^2 by intravenous [IV] push, days 1, 8, and 15; doxorubicin [D] at 75 mg/m^2 , IV infusion over 48 hours, day 1; cyclophosphamide [C] 1,200 $\text{mg/m}^2/\text{d}$, days 1 and 2, IV infusion over 1 hour; and mesna at 360 mg/m^2 in four doses by continuous infusion or bolus at regular intervals). Ifosfamide-etoposide (IE) cycles 2 and 4 (ifosfamide [I] at 1,800 $\text{mg/m}^2/\text{d} \times 5$ days, IV over 1 hour; etoposide [E] at 100 $\text{mg/m}^2/\text{d} \times 5$ days, IV over 1 hour; and mesna at 360 mg/m^2 in four doses by continuous infusion or bolus at regular intervals). Growth factor: pegfilgrastim at 100 $\mu\text{g/kg}$ subcutaneously [SC] by single injection 24 hours after completion of chemotherapy; filgrastim at 5 $\mu\text{g/kg/d}$ SC daily 24 hours after completion of chemotherapy per package insert until absolute neutrophil count [ANC] recovery ($\text{ANC} \geq 10 \times 10^9/\text{L}$) or 24 hours before the next cycle.

count (ANC) of $\geq 10 \times 10^9/L$ was achieved or until 24 hours before the next scheduled chemotherapy cycle, whichever occurred first. Patients randomly assigned to pegfilgrastim received $100 \mu\text{g/kg}$ subcutaneously approximately 24 hours after chemotherapy completion. Dose escalation of pegfilgrastim was to be considered for an age stratum if more than one of the six patients failed to achieve ANC recovery ($\text{ANC} \geq 0.5 \times 10^9/L$) in cycle 1. An age stratum was closed to accrual after two successive groups of six patients (within the age stratum) achieved ANC recovery. Thus, a minimum of 42 patients (12 pegfilgrastim and two filgrastim in each of the three age strata) were required to complete study-specified enrollment.

Therapy Guidelines

Four cycles of chemotherapy were administered at 3-week intervals. Mesna was used during all cycles for prevention of hemorrhagic cystitis. An $\text{ANC} \geq 1 \times 10^9/L$ and a platelet count $\geq 100 \times 10^9/L$ were required to start each cycle. Chemotherapy doses were modified for infection only if the episode required intensive care support or was associated with typhlitis, meningitis, or pneumonia with oxygen dependence.

Laboratory Monitoring

In cycles 1 and 3, weekly chemistry panels and daily complete blood counts (CBCs) were performed until the ANC exceeded $0.5 \times 10^9/L$ on two consecutive measurements. In cycles 2 and 4, both chemistry panels and CBCs were performed weekly. A CBC sample was also obtained 1 and 3 months after completion of cycle 4 laboratory monitoring. Serum samples for antibody testing were obtained before initiation of chemotherapy, at the end of treatment, and at the 1- and 3-month follow-up visits. A surface plasmon resonance Biacore 3000 (Biacore, Piscataway, NJ) affinity assay was used to quantify antibodies capable of binding to filgrastim and pegfilgrastim. The assay was performed according to the manufacturer's instructions. All samples positive for binding antibodies were tested for neutralizing antibodies using a cell-based neutralizing antibody assay. Pharmacokinetic samples were collected in cycles 1 and 3 before injection and 1, 2, and 4 hours after injection of pegfilgrastim or the first dose of filgrastim, and daily concurrently with CBC sample collections.

Statistical Analysis

This study was conducted to assess and provide preliminary comparison of the pharmacodynamic, pharmacokinetic, and safety profiles of a single dose of pegfilgrastim and daily doses of filgrastim in pediatric sarcoma patients. The calculations for sample size were based on an assumption of normally distributed durations of neutropenia, as previously documented in other studies.^{13,30} The primary efficacy end point was the duration of grade 4 neutropenia ($\text{ANC} < 0.5 \times 10^9/L$) during cycles 1 and 3. The minimum sample size (36 pegfilgrastim-treated and six filgrastim-treated patients) would allow the difference in duration of grade 4 neutropenia between the two treatment groups to be estimated with a distance from the estimate to the 95% confidence bounds of 1.3 days (assuming a standard deviation of 1.5 days) for cycles 1 and 3. Time to ANC recovery to $\geq 0.5 \times 10^9/L$ in cycles 1 and 3 and rate of febrile neutropenia (FN; defined as $\text{ANC} < 0.5 \times 10^9/L$ and an oral or oral-equivalent temperature $\geq 38.2^\circ\text{C}$ on the same day) were also assessed. Safety was evaluated across all four chemotherapy cycles.

Descriptive statistics were used to summarize the duration of grade 4 neutropenia, time to ANC recovery, proportion of patients without ANC recovery by day 21, and proportion of patients with FN in cycles 1 and 3 for each age cohort. For patients who did not experience grade 4 neutropenia in a given cycle, duration of neutropenia was assigned a value of 0. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 9.0) and were summarized by grade, relationship to study drugs, and treatment group.

Noncompartmental pharmacokinetic parameters were estimated on the basis of individual serum concentration data using WinNonlin Professional (Pharsight, Mountain View, CA) software. The maximum concentration (C_{max}) and the time it occurred (t_{max}) following dosing were recorded. A log-linear trapezoidal method was used to estimate the area under the (concentration-time) curve (AUC). $\text{AUC}_{0-\text{last}}$ was calculated from time zero to the time of the last measurable concentration (Ct). The first-order terminal rate constant (kel) was estimated via linear regression of the terminal log-linear

delay phase. Terminal half-life ($T_{1/2}$) was calculated as $\ln(2)/\text{kel}$. $\text{AUC}_{0-\infty}$ was estimated as the sum of corresponding $\text{AUC}_{0-\text{last}}$ and Ct/kel values.

RESULTS

Patients

This study was conducted between 2000 and 2007. Ten centers in the United States and Australia enrolled 44 patients, with 38 patients randomly assigned to pegfilgrastim and six randomly assigned to filgrastim. Table 1 shows baseline demographic and disease features of the study population. The median age, age distribution, race/ethnicity, weight, baseline ANC, and baseline platelet counts were similar in patients enrolled in the two treatment arms. This trial was initiated before the International Conference on Harmonisation guideline requiring a separate age stratum for children 0 to 2 years of age was developed³²; therefore, results are presented by protocol-specified age strata. Four patients between the ages of 28 days and 23 months were enrolled in the study.

Only 37 of the 38 patients randomly assigned to receive pegfilgrastim received study drug (Fig 1); one patient was withdrawn before pegfilgrastim administration because of concerns about protocol-required blood draws. Thirty-two (84%) patients randomly assigned to pegfilgrastim and three (50%) patients randomly assigned to filgrastim completed all planned cycles of chemotherapy and study drug treatment (Fig 1).

Table 1. Patients' Baseline Demographic and Disease Characteristics

Characteristic	Filgrastim (n = 6)		Pegfilgrastim (n = 38)	
	No.	%	No.	%
Sex				
Female	4	67	12	32
Male	2	33	26	68
Age, years				
Median	11.0		10.5	
Range	4.0-18.0		0.67-21.0	
Age group, years				
0-5	1	17	12	32
6-11	2	33	10	26
12-21	3	50	16	42
Race/ethnicity				
White	5	83	30	79
Black	0		3	8
Hispanic	1	17	4	11
Other	0		1	3
Disease				
Ewing sarcoma family of tumors	4	67	32	84
Rhabdomyosarcoma	1	17	3	8
Other soft tissue sarcoma	1	17	3	8
Weight, kg				
Median	46.7		44.6	
Range	17.8-84.8		7.9-119.2	
Baseline ANC, $\times 10^9/L$				
Median	3.96		4.16	
Range	3.55-8.50		1.27-13.88	
Baseline platelet count, $\times 10^9/L$				
Median	270		385.5	
Range	172-353		149-859	

Abbreviation: ANC, absolute neutrophil count.

Table 2. Efficacy Endpoints in Cycles 1 and 3

Efficacy Endpoint	Pegfilgrastim									
	Filgrastim		All		0-5 Years		6-11 Years		12-21 Years	
	No.	%	No.	%	No.	%	No.	%	No.	%
Cycle 1	n = 6		n = 37		n = 12		n = 10		n = 15	
Duration of grade 4 neutropenia, days										
Median	6.0		5.0		8.0		6.0		4.0	
Range	0-9		0-24		4-24		4-8		0-7	
Time to ANC recovery, days										
Median	14		14		15		14		13	
Range	12-16		10-31		12-31		12-16		10-15	
Patients without ANC recovery by day 21	0		1	3	1	8	0		0	
Febrile neutropenia	5	83	21	57	9	75	7	70	5	33
Cycle 3	n = 4		n = 34		n = 11		n = 10		n = 13	
Duration of grade 4 neutropenia, days										
Median	7.0		7.0		9.0		7.5		5.0	
Range	0-9		0-23		4-23		3-23		0-8	
Time to ANC recovery, days										
Median	15		14		17		14		13	
Range	15-17		11-28+		12-28+		11-20+		11-17	
Patients without ANC recovery by day 21	0		3	9	2	18	1	10	0	
Febrile neutropenia	3	75	15	44	7	64	4	40	4	31

NOTE. Censored value indicated by "+." Abbreviation: ANC, absolute neutrophil count.

Efficacy

Efficacy analysis (Table 2) included data for all 43 patients who received at least one dose of study drug. Appendix Table A2 (online only) reports on the intent-to-treat data set for the study's primary endpoint: duration of severe neutropenia. The study was designed as an estimation (hypothesis-forming) study, rather than as a hypothesis-testing study. In the first cycle of chemotherapy, median duration of grade 4 neutropenia was 5.0 days in the pegfilgrastim group and 6.0 days in the filgrastim group. Median duration of grade 4 neutropenia was similar in the third cycle of chemotherapy (7.0 days for both pegfilgrastim and filgrastim).

Over the course of the study, 25 (68%) of 37 patients in the pegfilgrastim group and five (83%) of six patients in the filgrastim group experienced FN. The median time to ANC recovery during cycle 1 of chemotherapy was 14 days in both treatment groups, with similar median recovery times in cycle 3 (Table 2).

In cycle 1, only one (3%) of 37 patients treated with pegfilgrastim failed to manifest neutrophil recovery. Among patients receiving pegfilgrastim, median duration of grade 4 neutropenia was inversely related to age group (ie, patients in the younger age groups experienced a longer median duration of grade 4 neutropenia) in both cycles 1 and 3.

Pharmacokinetics

The pharmacokinetic analysis included data for all patients who received at least one dose of study drug and had more than 50% of pharmacokinetic samples collected (n = 40; 34 pegfilgrastim and six filgrastim). The maximum median pegfilgrastim concentration was achieved approximately 24 to 48 hours after pegfilgrastim administration and was sustained until the ANC nadir was reached (Figs 3A-3C). As the ANC started to recover, pegfilgrastim concentration declined rapidly, consistent with neutrophil-mediated clearance.

Median drug exposures in cycle 3 were lower than those in cycle 1 for each age cohort.

Figures 3D and 3E show the median pharmacokinetic and ANC profiles of pegfilgrastim and filgrastim in cycles 1 and 3 for patients age 6 to 11 years. Compared with the serum pegfilgrastim concentration profile, the median serum filgrastim concentration declined rapidly after the first dose. After repeated administration, the daily trough filgrastim concentration increased until the ANC nadir occurred. Both pegfilgrastim and filgrastim serum concentrations declined rapidly after ANC recovery, consistent with neutrophil-mediated drug clearance. After the nadir, the ANC rise was gradual in patients treated with pegfilgrastim. Patients receiving filgrastim experienced elevations of ANC beyond the normal range because of continued filgrastim dosing during the neutrophil recovery phase. The youngest and oldest age cohorts had similar profiles (data not shown).

Pharmacokinetic parameters were determined for pegfilgrastim only. For filgrastim, the data were not sufficient for determination of pharmacokinetic parameters. The youngest cohort (0-5 years) had a higher exposure to pegfilgrastim than the other two cohorts (6-11 years and 12-21 years; Table 3), likely related to the fact that these younger patients experienced a longer duration of neutropenia (Table 2).

Safety

Safety analysis included data for all 43 patients who received at least one dose of study drug. Consistent with expectations for pediatric patients receiving myelosuppressive sarcoma chemotherapy, most patients (84% pegfilgrastim, 83% filgrastim) had one or more grade 3 or higher AEs (Table 4). Most AEs were attributed to the underlying disease process or the chemotherapy administered. AEs attributable to study drug were reported for 22% and 33% of patients who received pegfilgrastim and filgrastim, respectively. Bone pain was the most

Fig 3. Pharmacokinetic and absolute neutrophil count (ANC) profiles in cycles 1 and 3. Pegfilgrastim profiles after 100 $\mu\text{g/kg}$ pegfilgrastim administration to patients in the following age groups: (A) 0 to 5 years, (B) 6 to 11 years, and (C) 12 to 21 years. Pharmacokinetic and ANC profiles in patients in the 6 to 11 years age group receiving (D) pegfilgrastim and (E) filgrastim. Conc, concentration. (*) Number of patients beginning cycle 3.

common AE (11% pegfilgrastim, 17% filgrastim); other AEs were consistent with the known effects of these drugs. There were no significant differences in the overall safety profile noted between treatment arms or across age groups in the pegfilgrastim treatment arm. One fatal AE (respiratory acidosis in a patient who received pegfilgrastim) was noted; however, it was considered to be unrelated to pegfilgrastim by the investigator.

Antibody analysis included data for all patients who received study drug and had one or more antibody samples available ($n = 41$; 36 pegfilgrastim and five filgrastim). Ten (24%) of these 41 patients tested positive for binding antibodies against filgrastim or pegfilgrastim at baseline before study drug administration. Five of these patients also tested positive for neutralizing antibodies at baseline but became antibody negative after initiation of chemotherapy. One (2%) patient developed transient binding antibodies against filgrastim at a single time point after receiving pegfilgrastim but tested negative for pegfilgrastim neutralizing antibodies. The presence of

antibodies had no apparent effect on clinical outcomes or the pharmacokinetics of pegfilgrastim.

DISCUSSION

Randomized clinical trials in both children and adults have demonstrated that filgrastim prophylaxis for chemotherapy-induced neutropenia results in reduction of the depth of the ANC nadir,^{12,33} duration of grade 4 neutropenia,^{13,14} number of episodes of FN,^{15,34} number and duration of hospitalizations,^{13,33,35} number of documented infections,^{12,15,33,35} and use of antibiotics.^{13-15,36} Filgrastim use has become routine in the management of pediatric sarcomas requiring chemotherapy.^{4-6,11,25}

Our study indicates that pegfilgrastim 100 $\mu\text{g/kg}$ administered once per chemotherapy cycle has similar efficacy and safety to filgrastim at 5 $\mu\text{g/kg}$ administered daily in pediatric patients receiving

Table 3. Pegfilgrastim Pharmacokinetic Parameter Values in Cycles 1 and 3 After Administration of 100 µg/kg Pegfilgrastim to Pediatric Patients

Summary Statistic	C _{max} (ng/mL)		t _{max} (hours)		AUC _{0-∞} (ng · h/mL)		t _{1/2} (hours)	
	Mean	SD	Median	Range	Mean	SD	Mean	SD
0-5 years								
Cycle 1 (n = 11)	401	190	48.0	24.0-216.0	47,900	22,500	30.1	38.2
Cycle 3 (n = 10)	311	208	24.0	4.0-96.0	36,300	30,400	30.8	19.9
6-11 years								
Cycle 1 (n = 10)	205	146	24.0	24.0-144	22,000	13,100	20.2	11.3
Cycle 3 (n = 9)	204	142	24.0	4.0-120.0	21,200	14,500	23.1	13.5
12-21 years								
Cycle 1 (n = 13)	229	176	48.0	24.0-144.0	29,300	23,200	21.2	16.0
Cycle 3 (n = 13)	171	102	24.0	4.0-120.0	20,300	14,300	19.3	10.2

NOTE. The extrapolated area under the concentration-time curve (AUC) for AUC_{0-∞} calculation was less than 1%.

Abbreviations: C_{max}, maximum serum concentration; t_{max}, time to maximum serum concentration; t_{1/2}, terminal half-life; SD, standard deviation.

sarcoma-directed chemotherapy (VDC/IE). Median duration of grade 4 neutropenia was 5.0 days in the pegfilgrastim group and 6.0 days in the filgrastim group in cycle 1 and 7.0 days for both groups in cycle 3. Over the course of the study, FN occurred in similar proportions of patients in the two treatment groups (68% pegfilgrastim; 83% filgrastim). Two studies^{11,25} that used a similar dose-intensive regimen of VDC/IE in pediatric patients reported a median duration of grade 4 neutropenia of 5.0 days for pegfilgrastim and 6.0 days for filgrastim, a difference that was not clinically significant. Wexler et al¹¹ also reported a similar incidence of FN in patients receiving pegfilgrastim and filgrastim (57% and 83%, respectively) after chemotherapy cycle 1. Of note, our study included a younger patient population (from 28

days to 21 years of age, compared with 1 to 25 years in Wexler et al¹¹ and 3 to 25 years in Fox et al²⁵).

Pharmacokinetic profiles of pegfilgrastim and filgrastim in this study are consistent with those in adults.^{22,30,31,37} Whereas filgrastim is cleared by neutrophils and predominantly by the kidneys, thus having a relatively short serum half-life, pegfilgrastim is cleared almost exclusively by neutrophils.¹⁸⁻²⁰ Serum concentrations of pegfilgrastim are therefore sustained throughout the ANC nadir, with rapid clearance of the drug on neutrophil recovery. Neutrophil recovery, defined as an ANC $\geq 0.5 \times 10^9/L$ after nadir, occurred in 36 of 37 patients during cycle 1; the single patient without neutrophil recovery was in the 0-5 years age group. Median drug exposures in cycle 3 were lower than those in cycle 1. This finding may be explained by the expansion of neutrophils and neutrophil precursor mass over time leading to more rapid drug clearance, consistent with a neutrophil-mediated clearance mechanism.³⁸ Among patients receiving pegfilgrastim, those in the 0-5 years age group experienced a longer median duration of neutropenia than older patients. Since the youngest patient cohort also had a higher median exposure to pegfilgrastim than did the other two cohorts, the more protracted neutropenia experienced by the youngest children in this study is likely to be due to a greater relative exposure to myelosuppressive chemotherapy rather than to inadequate pegfilgrastim dosing. However, caution should be exercised regarding comparisons between age groups because of the small sample sizes.

All patients in the 0-5 years age group received chemotherapy dosing according to body-surface area, although, per protocol guidelines, patients who were ≤ 1 year of age or weighed ≤ 10 kg could be dosed according to institutional guidelines. When chemotherapy doses were examined by weight (Appendix Table A3, online only), the doses of doxorubicin and cyclophosphamide that were received by the youngest age group were higher than those received by both older age groups and nearly 50% higher than those received by the oldest age group. Similar findings (maintenance of serum pegfilgrastim concentrations in the setting of prolonged neutropenia after highly myelosuppressive chemotherapy) have been observed in adults treated for acute myeloid leukemia.³⁷

Most patients experienced grade 3 or higher AEs, as is expected for pediatric patients receiving VDC/IE chemotherapy for treatment of sarcoma.¹¹ Twenty-two percent of patients who received pegfilgrastim and 33% of patients who received filgrastim experienced AEs

Table 4. Severe, Life-Threatening, or Fatal (Grade 3 to 5) Adverse Events Experienced by More Than One Patient

Adverse Event	Filgrastim (n = 6)		Pegfilgrastim (n = 37)	
	No.	%	No.	%
Total No. of patients reporting severe, life-threatening, or fatal adverse events	5	83	31	84
Febrile neutropenia	4	67	21	57
Anemia	2	33	21	57
Neutropenia	0		6	16
Thrombocytopenia	0		6	16
Vomiting	0		4	11
Catheter-related infection	0		4	11
Alopecia	1	17	3	8
Constipation	0		3	8
Diarrhea	1	17	2	5
Pyrexia	1	17	2	5
Dehydration	1	17	2	5
Colitis	0		2	5
Otitis media	0		2	5
Decreased platelet count	0		2	5
Anorexia	0		2	5
Hypokalemia	0		2	5
Anxiety	0		2	5
Hallucination	0		2	5
Hypoxia	0		2	5
Respiratory distress	1	17	1	3

attributed to growth factor use, of which bone pain was the most common. Studies in adults have documented similar AE profiles; mild to moderate bone pain is among the most common documented AEs.^{30,31,37} In our pediatric patients treated with pegfilgrastim, there was no evidence of differences in toxicity across the three age groups. Although about one quarter of patients had antibodies against filgrastim or pegfilgrastim at baseline and one patient developed transient antibodies to filgrastim after receiving pegfilgrastim, these antibodies had no apparent effect on clinical outcomes or the pharmacokinetics of pegfilgrastim. Seroreactivity has been documented in adults receiving pegfilgrastim, but the presence of antibodies has not had any clinical sequelae.²²

Growth factor use results in a relative decrease in the incidence of rather than absolute prevention of FN. This study suggests that a single injection of 100 $\mu\text{g/kg}$ pegfilgrastim is similar to daily injections of filgrastim at 5 $\mu\text{g/kg}$ for the reduction of chemotherapy-induced neutropenia and its associated complications in pediatric patients receiving myelosuppressive chemotherapy. Administration of a single dose of growth factor with self-regulated clearance is likely to be of substantial benefit in the pediatric population. Although no published data exist, clinical experience has shown that eliminating the need for daily injections may improve patient and family compliance, lead to fewer growth factor therapy interruptions, and decrease the burden of therapy on both the child and the family.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

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