Published in final edited form as:

Clin Cancer Res. 2009 December 1; 15(23): 7361–7367. doi:10.1158/1078-0432.CCR-09-0761.

Randomized trial and pharmacokinetic study of pegfilgrastim vs. filgrastim after dose-intensive chemotherapy in young adults and children with sarcomas

Elizabeth Fox¹, Brigitte C. Widemann¹, Douglas S. Hawkins², Nalini Jayaprakash¹, Ramzi Dagher¹, Alberta A. Aikin¹, Donna Bernstein¹, Lauren Long¹, Crystal Mackall¹, Lee Helman¹, Seth M. Steinberg³, and Frank M. Balis¹

¹ Pediatric Oncology Branch, CCR, NCI, Bethesda, MD

² Seattle Children's Hospital, Seattle, WA

³ Biostatistics & Data Management Section, CCR, NCI, Bethesda, MD

Abstract

Purpose—To compare the effectiveness, tolerance and pharmacokinetics of a single dose of pegfilgrastim to daily filgrastim in children and young adults with sarcomas treated with dose-intensive combination chemotherapy.

Experimental Design—Patients were randomized to receive a single dose of 100 mcg/kg of pegfilgrastim subcutaneously or 5 mcg/kg/day of filgrastim subcutaneously, daily until neutrophil recovery after 2 treatment cycles with vincristine, doxorubicin, and cyclophosphamide (VDC) and 2 cycles of etoposide and ifosfamide (IE). The duration of severe neutropenia (ANC $\leq$ 500/mcL) during cycles 1–4 and cycle duration for all cycles were compared. Pharmacokinetics of pegfilgrastim and filgrastim and CD34+ stem cell mobilization were studied on cycle 1. Growth factor related toxicity, transfusions, and episodes of fever and neutropenia and infections were collected for cycles 1–4.

Results—Thirty-four patients (median age 20 years, range 3.8–25.8) were enrolled, 32 completed cycles 1–4. The median (range) duration of ANC $<$ 500/mcL was 5.5 (3–8) days for pegfilgrastim and 6 (0–9) days for filgrastim ($p = 0.76$) after VDC, and 1.5 (0–4) days for pegfilgrastim and 3.75 (0–6.5) days for filgrastim ($p = 0.11$) after IE. More episodes of febrile neutropenia and documented infections occurred on the filgrastim arm. Serum pegfilgrastim concentrations were highly variable. Pegfilgrastim apparent clearance (11 ml/h/kg) was similar to that reported in adults.

Corresponding Author: Elizabeth Fox, Pharmacology & Experimental Therapeutics Section, Pediatric Oncology Branch, CCR, NCI, 1-5750, 10 Center Dr. MSC 1101, Bethesda, MD 20892, Phone: 301-402-6641, Fax: 301-480-8870, foxb@mail.nih.gov.

Preliminary results from this trial were previously presented at the 2006 Annual Meeting of the American Society for Clinical Oncology, Atlanta, GA

Statement of Translational Relevance

This manuscript reports the randomized study of pegfilgrastim vs. filgrastim in children and young adults with newly diagnosed sarcoma. The results encompass the primary clinical outcome (number of days of severe neutropenia) and toxicity profile, as well as laboratory correlates including pharmacokinetic analysis of pegfilgrastim and filgrastim, pharmacodynamic correlation with absolute neutrophil count, mobilization of CD34+ cells, monitoring for antibody production. This work demonstrates that in newly diagnosed patients with sarcoma the duration of neutropenia is similar when using pegfilgrastim vs filgrastim. In addition to the advantage of once per cycle administration, pegfilgrastim is better tolerated and results in fewer hospitalizations for infection, fever and neutropenia. The relationship of serum growth factor concentrations to neutrophil recovery and the difference in the neutrophil kinetics between filgrastim and pegfilgrastim treated subjects verifies that pegylation of filgrastim substantially alters pharmacokinetics and allows for once per cycle dosing in this population.

Conclusion—A single dose per cycle of pegfilgrastim was well tolerated and may be as effective as daily filgrastim based on the duration of severe neutropenia and number of episodes of febrile neutropenia and documented infections after dose-intensive treatment with VDC and IE.

INTRODUCTION

Pegfilgrastim (filgrastim-SD/01, Neulasta™), which is a sustained-duration formulation of filgrastim, is FDA approved at a fixed dose of 6 mg subcutaneous injection once per treatment cycle for adults and children >45 kg to shorten the duration of chemotherapy-induced neutropenia. Pegfilgrastim has a 20-kDa polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionyl residue of filgrastim. PEG is inert, has low antigenicity, minimal toxicity, and alters the clearance of the agent. Filgrastim (clearance, 40 ml/hr/kg) is eliminated primarily by renal excretion, whereas pegfilgrastim elimination (clearance, 14 ml/hr/kg) is dependent on receptor binding to neutrophils.[1] As a result, pegfilgrastim is self-regulating because it persists in the body during neutropenia but is cleared rapidly when the neutrophil count recovers.[2,3]

The safety and efficacy of pegfilgrastim has been demonstrated in large randomized trials in adults with non-myeloid cancers that were treated with myelosuppressive chemotherapy.[1, 4–7] Incidence and duration of neutropenia and side effects were similar to daily filgrastim. The pharmacokinetic profile of pegfilgrastim in adults is nonlinear.[8] In 379 adults with cancer, the pegfilgrastim apparent clearance was highly variable and dependent on dose and neutrophil count.[2] The terminal half-life ranges from 46–62 hours in normal volunteers.

Primary prophylaxis with myeloid growth factors is frequently utilized in children and adolescents receiving dose-intensive chemotherapy.[9–11] In children, several small uncontrolled studies and case series describing the use of pegfilgrastim have been reported. [12–15] Spunt et al. have reported preliminary results from a trial conducted in children <21 years old with sarcoma randomized to receive pegfilgrastim (n=14) or filgrastim (n=2) after dose-intensive chemotherapy. Preliminary data suggests that once per cycle dosing with pegfilgrastim (100 mcg/kg) resulted in similar severity and duration of post-chemotherapy neutropenia to daily filgrastim (5 mcg/kg).[16]

We conducted a trial of pegfilgrastim in children and young adults with newly diagnosed sarcoma. Patients were randomized (1:1) at the time of study enrollment to receive pegfilgrastim or filgrastim after multi-agent, dose-intensive chemotherapy in order to determine if the time to neutrophil recovery was equivalent between the two arms. The study was also designed to assess the tolerance and toxicity of pegfilgrastim, compare the pharmacokinetics (PK) of pegfilgrastim and filgrastim, and compare CD34+ stem cell mobilization between the two arms.

PATIENTS AND METHODS

Study Treatment

This trial was performed under an Investigator IND. Pegfilgrastim and filgrastim were manufactured and provided by Amgen (Thousand Oaks, CA). Pegfilgrastim was provided in single-use, preservative-free vials as a sterile 1.2 mL solution at concentration of 10 mg/mL. This pegfilgrastim formulation allowed for individualized dosing based on body weight.

The chemotherapy treatment plan is described in Table 1. Patients were randomized at study entry to receive pegfilgrastim (100 mcg/kg subcutaneously as a single dose 24–36 hours after completion of each cycle of chemotherapy) or filgrastim (5 mcg/kg/day subcutaneously, daily starting 24 hours and continuing until the post-nadir neutrophil count was $\geq 10,000/\text{mcL}$ after

each cycle of chemotherapy). Randomization was performed centrally and was not stratified for age, diagnosis or other baseline characteristics. For each patient, the treatment assignment (pegfilgrastim vs. filgrastim) was maintained throughout all treatment courses. Supportive care measures also included mesna as a uroprotectant with cyclophosphamide and ifosfamide and dexrazoxane as a cardioprotectant prior to doxorubicin. Surgery or radiation directed against the primary tumor commenced after cycle 5. Fourteen cycles (6 VDC and 8 IE) were planned.

If a treatment cycle was delayed for >7 days to allow for recovery from myelosuppression caused by the prior cycle's treatment, subsequent doses of the myelotoxic drugs that caused the prolonged myelosuppression were reduced by 25% on subsequent cycles of the same type of therapy. Dose modifications were not based on the nadir of the neutrophil or platelet counts or on the duration of grade 4 neutropenia and thrombocytopenia, unless it delayed the next treatment cycle by >7 days.

Subject Eligibility

Patients <26 years old with Ewing sarcoma family of tumors, alveolar rhabdomyosarcoma, stage 3 or 4 embryonal rhabdomyosarcoma, and unresectable or metastatic malignant peripheral nerve sheath tumor or synovial sarcoma were eligible. Normal cardiac (left ventricular ejection fraction) and renal function, absolute neutrophil count $\geq 1,500/\text{mcL}$, hemoglobin $\geq 9 \text{ g/dL}$, and platelet count $\geq 100,000/\text{mcL}$ were required. Patients who had received prior chemotherapy or radiation therapy, patients with tumor infiltration of bone marrow determined by biopsies and patients who were pregnant or breastfeeding were excluded. All patients or their parent or guardian signed an informed consent document. Assent of minors was obtained according to institutional guidelines. The study was approved by Institutional Review Boards at the participating sites.

Statistical Considerations

The primary objective of this trial was to determine whether the duration of chemotherapy-induced severe neutropenia (absolute neutrophil count $<500/\text{mcL}$) was non-inferior for the pegfilgrastim arm compared with the filgrastim arm for the first four cycles of chemotherapy (no more than one standard deviation longer for pegfilgrastim). The sample size was estimated based upon standard methods for a two group t-test of equivalence of mean with equal standard deviations and sample sizes per arm, but controlling for two comparisons as noted below. Specifically, separately for two V₃DC cycles averaged together and two IE cycles averaged together, when the sample size in each arm is 17, for each set of averaged cycles, a two-group 0.025 one-sided t-test will have 80% power to reject the null hypothesis of inferiority (that the average duration of severe neutropenia on the pegfilgrastim arm was at least one standard deviation longer than that on the filgrastim arm) in favor of an alternative that the mean of the pegfilgrastim arm is not inferior to that of filgrastim, that is, that the average durations of neutropenia on the two arms do not differ by more than 1.0 standard deviation (which is presumed to be equal in both arms). Based on data from previous institutional experience using these chemotherapy regimens in this population, the variance in the duration of severe neutropenia was 2 days.[17,18] Although this determination was based on an assumption that the durations of severe neutropenia would be normally distributed, this was not the case for the IE cycles. Thus, for simplicity, a Wilcoxon rank sum test was used to test if the duration of neutropenia differed significantly (overall $p<0.05$) between the arms when the durations from the two V₃DC cycles and the two IE cycles were averaged and tested separately. Differences in toxicity, pharmacokinetic parameters, CD34 stem cell mobilization, and days of febrile neutropenia, were also compared by the Wilcoxon rank sum test. Differences in duration of neutropenia between the V₃DC and IE cycles were tested for statistical significance by a Wilcoxon signed rank test, separately for the two treatment arms. All p-values are two-tailed and are presented without adjustment for multiple comparisons.

Neutrophil Recovery and Cycle Duration

Severe neutropenia was defined as an absolute neutrophil count (ANC) $<500/\text{mcL}$ and recovery was defined as a post-nadir ANC $\geq 500/\text{mcL}$. The primary endpoint was determined during the first 4 treatment cycles (2 $V_3\text{DC}$ cycles followed by 2 IE cycles) to avoid potential confounding effects of radiation therapy on bone marrow function. Complete blood counts (CBC) were performed at least thrice week during cycles 1–4 and at least twice weekly during cycles 5–14. Cycle duration was calculated for each cycle as the number of days from day 1 of the cycle to day 1 of the subsequent cycle. Cycles commenced at 21 day intervals if the patient had recovered from treatment-related toxicity from the prior cycle. For non-hematologic toxicities, recovery was defined as NCI Common Toxicity Criteria (CTC v.2) grade ≤ 1 ; and for hematologic toxicity, the ANC had to be $\geq 500/\text{mcL}$ and the platelet count $\geq 75,000/\text{mcL}$. Criteria for the administration of red blood cell and platelet transfusions were not specified in the protocol. The use of other growth factors (GM-CSF, erythropoietin, IL-11) was prohibited.

Adverse Events

Toxicity was graded using the CTC v.2 (<http://ctep.info.nih.gov>). All adverse events attributed to growth factors that occurred during the study, as observed by the investigator or reported by the subject, were recorded. Toxicity possibly, probably or definitely related to pegfilgrastim or filgrastim, hospitalization for fever and neutropenia, number of red cell and platelet transfusions, mucositis, and documented or suspected infections are reported for cycles 1 to 4.

Pharmacokinetics (PK), Stem Cell Mobilization and Antibody Production

Serum samples were obtained prior to and 1, 2, 4, 6, 8, 24, and 28 hours after first dose of filgrastim and pegfilgrastim in all patients. For pegfilgrastim, samples were also obtained at 96, 144, 192, 240, and 504 hr. For filgrastim, additional trough samples were obtained on days 4, 6, 8, 10 and 4 hours after the day 10 dose. Serum granulocyte colony stimulating factor (G-CSF) concentrations were measured using an ELISA (R&D Systems, Minneapolis, MN).^[19] The lower limit of quantification was 0.04 ng/mL. Pharmacokinetic parameters were calculated using non-compartmental methods.¹

Quantification of CD34+ stem cells was performed using flow cytometry of EDTA whole blood drawn on the day that the post-nadir neutrophil count first exceeded 500/mcL during cycle 1.

Binding antibody immunoassay (Biacore 3000, BIAcore AB, Sweden) was used to detect antibodies capable of binding to pegfilgrastim in patients' serum at baseline and prior to each cycle (post-exposure) of therapy by exposure of patient serum samples to biosensor with drug covalently immobilized to a surface. Antibodies were detected by accumulation of mass on the surface and confirmed by anti-immunoglobulin reagent. Post-exposure response in the binding antibody immunoassay of ≥ 2 -fold higher than baseline was considered positive. In samples positive for binding antibody, a cell-based neutralizing antibody assay was used to determine if serum contained antibodies capable of neutralizing pegfilgrastim. Using a cell line that required granulocyte growth factor and interleukin-3 for growth, neutralizing antibody was measured in patient's serum when cell growth was inhibited in the presence of patients serum.

¹Blode H, Brett M, Buhrens KG, et al. Collection of terms, symbols, equations, and explanations of common pharmacokinetic and pharmacodynamic parameters and some statistical functions. AGAH Working Group PK-PD Modeling 2004 [cited; Available from: <http://www.agah.info/en/the-agah/publications.html>]

RESULTS

Patient Characteristics

Thirty-four total patients were enrolled, 29 at the Pediatric Oncology Branch, NCI and 5 at Seattle Children's Hospital, Seattle, WA between December 2000 and December 2005. Patient characteristics are listed in Table 2. Two patients in the pegfilgrastim arm did not complete the initial 4 cycles of chemotherapy. Neither patient discontinued therapy due to adverse events. One patient discontinued therapy after cycle 2 due to progressive tumor, and one withdrew consent after cycle 1 to transfer care to another institution.

For patients on the filgrastim arm, the median (range) number of daily doses of filgrastim was 13 (7–27) per cycle for the two V₃DC cycles and 10 (6–24) per cycle for the two IE cycles. Two children enrolled on the study were <5 years old, both randomized to filgrastim.

Neutrophil Recovery

The duration of severe neutropenia was significantly longer after V₃DC (cycles 1 and 2) than after IE (cycles 3 and 4) for both the pegfilgrastim ($p<0.001$) and filgrastim ($p<0.001$) treatment arms (Fig 1). Six of 15 patients on the pegfilgrastim arm and 5 of 14 patients on the filgrastim arm did not have an ANC <500/mcL documented during their initial two IE cycles.

The duration of severe neutropenia (ANC <500/mcL) for the mean of cycles 1 and 2 of V₃DC and the mean of cycles 3 and 4 of IE are presented in Fig 1 by treatment arm (pegfilgrastim vs. filgrastim). The duration of neutropenia could be definitively determined on 28 of the 34 enrolled patients during the two initial V₃DC cycles and on 29 patients during the two initial IE cycles. The inevaluable patients either did not complete the first 4 cycles of treatment ($n=2$) or did not have blood counts performed frequently enough to accurately determine the duration of severe neutropenia ($n=4$). During the first four cycles, the number of days of severe neutropenia was not significantly different between the two treatment arms for either V₃DC cycles (median 5.5, range 3–8 for pegfilgrastim vs. median 6.0, range 0–9 for filgrastim; $p=0.76$) or IE cycles (median 1.5, range 0–4 for pegfilgrastim vs. median 3.75, range 0–6.5 for filgrastim; $p=0.11$).

The cycle duration for all delivered cycles of therapy is presented in Table 2 and was a median of 21 days for both treatment arms for VDC cycles and for IE cycles. No patient required a dose reduction due to delayed recovery of blood counts. The majority of cycle delays were due to scheduling or complications of surgery or radiation on cycles 5–7.

The ANC profile after pegfilgrastim, which was characterized by higher pre-nadir than post-nadir ANC peaks, differed from that observed after filgrastim, which resulted in higher post-nadir ANC peaks (Fig 2). During cycles 1 and 2 and cycles 3 and 4, there were statistically significant differences in pre-nadir and post-nadir peak ANCs on the treatment arms. The median (range) pre-nadir ANC peak was 20,100/mcL (2,300 – 94,900/mcL) in the pegfilgrastim group and 10,700/mcL (1,400 – 39,400/mcL) in the filgrastim group ($p=0.024$); the median (range) post-nadir ANC peak was 8,000/mcL (2,400 – 28,200/mcL) in the pegfilgrastim arm and 20,400/mcL (2,200 – 47,400/mcL) in the filgrastim arm ($p<0.001$).

Twelve of 17 patients on the pegfilgrastim arm experienced 18 episodes (29% of cycles) of grade 3 fever and neutropenia requiring hospitalization during the first 4 cycles of chemotherapy compared to 15 of 17 patients and 32 episodes (47% of cycles) on the filgrastim arm. There were 4 documented infections on the pegfilgrastim arm, including 1 episode each of *S. aureus* bacteremia, *S. aureus* skin infection, *P. jiroveci* pneumonia, and *Enterobacter* sp. urinary tract infection. Eight documented infections occurred on the filgrastim arm, including one *E. coli* bacteremia, one *S. epidermitis* bacteremia, three episodes of

mucocutaneous candidiasis, one group A streptococcal pharyngitis, one *Enterbacter sp.* urinary tract infection, and one episode of pityrosporum folliculitis.

Stem Cell Mobilization

Mobilization of CD34+ stem cells did not differ between the two arms ($p=0.97$). The median (range) CD34+ cell count at the time of neutrophil recovery on cycle 1 (V₃DC) was 165/mcL (10–739/mcL) on the pegfilgrastim arm and 53/mcL (35–865/mcL) on the filgrastim arm.

Neutralizing Antibody

No neutralizing antibody to pegfilgrastim was detected in 16 patients (163 cycles) who were enrolled on the pegfilgrastim arm

Adverse Events

Pegfilgrastim and filgrastim were well tolerated in this patient population. Adverse events associated with growth factor administration on the first 4 cycles of chemotherapy were similar on the 2 treatment arms (Table 3). No dose modifications to growth factor therapy were required because of adverse events on either treatment arm. Twenty months after completion of chemotherapy, one patient on the pegfilgrastim arm developed acute leukemia with t(3;21), +21, -8, del 7 chromosomal abnormalities.

Pharmacokinetics

The mean ($n=17$) plasma concentration-time profile of pegfilgrastim is shown in Fig 2A. The serum concentration peaked 2 h after the dose and then declined in concert with the pre-nadir ANC peak. A secondary pegfilgrastim peak was observed after day 7 when the ANC approached its nadir. The serum pharmacokinetic parameters for pegfilgrastim and filgrastim are reported in Table 4. The terminal half-life of pegfilgrastim derived from the mean serum concentrations ($n=17$) was 49 h. Absorption (T_{max}) and apparent clearance (CL/F) were significantly different ($P<0.001$) in the pegfilgrastim compared to filgrastim arm. Substantial inter-subject variability was observed with both growth factors.

DISCUSSION

The duration of severe neutropenia after dose-intensive, combination chemotherapy for pediatric and young adult patients with sarcoma was similar for a single dose of pegfilgrastim (100 mcg/kg SC) and daily filgrastim injections (5 mcg/kg/d SC) in this relatively small study. This trial was designed to demonstrate that pegfilgrastim is not inferior to filgrastim, but, in fact, the parameters measured to assess the therapeutic effect of the two growth factors favored pegfilgrastim. The duration of severe neutropenia was shorter with pegfilgrastim, especially with IE, and there were fewer episodes of febrile neutropenia and fewer documented infections in patients receiving pegfilgrastim. These observations are similar to results in the meta-analysis of randomized trials in adults.[20]

Pegfilgrastim was well tolerated and had a toxicity profile similar to daily filgrastim. Growth factor-related bone pain and transient elevations in hepatic transaminases were observed in <14% of cycles on both arms. Episodes of mucositis and number of transfusions were also similar.

Pegfilgrastim's single injection per cycle dosing schedule provides a significant advantage over daily filgrastim injections for younger children, for whom needles and injections can cause substantial discomfort and distress. The single dosing schedule is also likely to result in improved compliance. These advantages reinforce the need to develop a formulation of pegfilgrastim that can be administered to children who weigh under 45 kg.

The combination of ifosfamide and etoposide was significantly less myelosuppressive than vincristine, cyclophosphamide and doxorubicin. The duration of severe neutropenia after IE was shorter than V₃DC on both treatment arms, and a substantial proportion (38%) of patients across both arms did not have a documented ANC <500/mcL after IE with thrice weekly monitoring of the blood counts. This suggests that higher doses of IE may be tolerable if it is administered with growth factor support.

The ANC profile with pegfilgrastim differed from the profile with filgrastim in that the peak ANC prior to the nadir was higher in patients receiving pegfilgrastim than in those receiving filgrastim, and the peak ANC after the nadir was higher on the filgrastim arm. Serum pharmacokinetics and neutrophil kinetics indicate that administration of pegfilgrastim results in higher serum G-CSF concentrations and neutrophil count early in the cycle, but this did not impair the rate of neutrophil recovery after the nadir. The absence of high peak in post-nadir neutrophil counts with pegfilgrastim reflects the self-regulatory, receptor-mediated clearance of pegfilgrastim. In contrast, high post-nadir ANC peaks are associated with daily filgrastim [21], in part related to the dosing algorithm, which requires continued daily dosing until the neutrophil count recovers to 10,000/mcL. Mobilization of CD34+ cells after V₃DC was similar in both cohorts and was similar to mobilization with pegfilgrastim after cyclophosphamide in adults.[22]

Pegfilgrastim serum concentrations were highly variable, which may reflect variability in the neutrophil count. The serum concentration peaked 24 h after the dose and then declined in concert with the pre-nadir peak in the neutrophil count due to receptor binding. The secondary peak in the pegfilgrastim serum concentration around day 7 (Fig 2A) may reflect release of the drug from receptors as the neutrophil count falls. The clearance of pegfilgrastim in this population (11 mL/h/kg) was similar to that reported in adults (14 mL/h/kg).[1] Clearance did not differ in patients receiving <6 mg compared to patients receiving ≥ 6 mg of pegfilgrastim. Filgrastim was absorbed more rapidly and cleared more rapidly than pegfilgrastim.

In conclusion, on this small randomized study, single dose per cycle of pegfilgrastim was well tolerated and was as effective as daily filgrastim based on the duration of severe neutropenia and number of episodes of febrile neutropenia and documented infections after dose-intensive treatment with V₃DC and IE. Future pediatric studies of pegfilgrastim should focus on the development and clinical testing of a formulation for patients <45 kg.

Acknowledgments

This research was supported, in part, by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research and by CTSA Grant Number I ULI RR025014-01 from the National Center for Research Resources (NCRR), a component of NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

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Fig 1.

The number of days of severe neutropenia in patients treated with pegfilgrastim compared to patients treated with filgrastim during (A) cycles 1 and 2 of V₃DC and (B) cycles 3 and 4 of IE. Symbols represents the average days of severe neutropenia during cycle 1 and 2 or 3 and 4 for each patient; the line is the median for each group.

Fig 2.

Absolute neutrophil counts (ANC) during cycles 1 and 2 of V₃DC on the pegfilgrastim arm (A) and the filgrastim arm (B) and cycles 3 and 4 of IE on the pegfilgrastim arm (C) and the filgrastim arm (D) for all patients. Geometric mean serum G-CSF concentration for patients receiving pegfilgrastim is presented for cycle 1 in panel A.

Table 1

Chemotherapy regimen

Regimen	Cycle [*]	Drug	Cycle Day
V ₃ DC	1, 2, 9, 13	Vincristine (V) 2 mg/m ² IV push (max, 2 mg)	1, 8, 15
		Doxorubicin (D) 37.5 mg/m ² IV over 15 min	1 and 2
		Cyclophosphamide (C) 1200 mg/m ² IV over 1 h	1 and 2
		Dexrazoxane 375 mg/m ² IV over 15–30 min prior to D	1 and 2
		Mesna 360 mg/m ² during C, immediately after C, and then q3h for 3 – 6 additional doses	1 and 2
V ₁ DC	5, 11	Vincristine 2 mg/m ² IV push (max, 2 mg)	1
		Doxorubicin 37.5 mg/m ² IV over 15 min	1 and 2
		Cyclophosphamide 1,200 mg/m ² IV over 1 h	1 and 2
		Dexrazoxane 375 mg/m ² IV over 15–30 min prior to D	1 and 2
		Mesna 360 mg/m ² during C, immediately after C, and then q3h for 6 additional doses	1 and 2
IE	3, 4, 6, 7, 8, 10, 12, 14	Etoposide (E) 100 mg/m ² IV over 60 min	1–5
		Ifosfamide (I) 1,800 mg/m ² IV over 60 min	1–5
		Mesna 360 mg/m ² during I, immediately after I, and then q3h for 6 additional doses	1–5

Abbreviations: V₃DC, vincristine (3 weekly doses), doxorubicin, cyclophosphamide; V₁DC, vincristine (single dose), doxorubicin, cyclophosphamide; IE, ifosfamide, etoposide

* Cycle duration was 21 days, but patients must have recovered (see text) from treatment-related toxicity on the prior cycle before starting the subsequent cycle.

Table 2**Patient characteristics**

Characteristic	Pegfilgrastim	Filgrastim
No. patients	17	17
Median (range) Age	17.9 (10.6–25.8)	18.9 (3.8–23.9)
Median (range) Baseline Characteristics		
Weight (Kg)	63.1 (39.4–101.1)	64.8 (16–97.6)
Absolute Neutrophil Count (cells × 10 ³ /mcL)	3.8 (2.3–10.2)	2.9 (2.5 – 5.1)
Platelet Count (platelets × 10 ³ /mcL)	272 (153–721)	296 (205–366)
Male: Female	11:6	6:11
Ethnicity		
White (Non-Hispanic)	12	10
Hispanic	3	5
African-American	2	1
Other	0	1
Diagnosis		
Ewing Sarcoma Family of Tumors	9	12
Alveolar Rhabdomyosarcoma	2	3
Embryonal Rhabdomyosarcoma	2	0
Malignant Peripheral Nerve Sheath Tumor	2	0
Synovial Sarcoma	2	2
Local Control		
Surgery	4	7
Radiation therapy	11	6
Off protocol therapy prior to local control	2	4
Treatment Summary		
No. patients completing cycles 1–4	15	17
Median (range) cycles/patient	9 (1–14)	14 (4–14)
VDC cycles		
Cycles 1 & 2 (No. delivered)	34	30
Cycle duration (Cycle 1&2), median (range)	21 (20–26)	21 (20–26)
% cycles ≤ 21d (Cycle 1 & 2)	82%	80%
% cycles >28d (Cycle 1 & 2)	0%	0%
Cycles 5, 9, 11, 13 (No. delivered)	42	43
Cycle duration, median (range)	21 (15–78)	23 (18–94)
% cycles ≤ 21 d	64%	42%
% cycles > 28 d	16%	23%
IE cycles		
Cycle 3 & 4 (No. delivered)	32	30
Cycle duration (Cycle 3&4), median (range)	21 (17–23)	21 (20–28)
% cycles (Cycle 3 & 4) ≤ 21d	81%	73%
% cycles (Cycles 3 & 4) >28d	0%	0%
Cycles 6, 7, 8, 10, 12, 14 (No. delivered)	59	64
Cycle duration, median (range)	21 (17–43)	22 (15–206)
% cycles ≤ 21d	63%	47%
% cycles >28d	17%	12.5%

Table 3

Growth factor-associated adverse events on cycles 1 to 4 by treatment arm

	Pegfilgrastim	Filgrastim
Patients/Cycles	17/63	17/68
Toxicity (Patients/Episodes)		
Mucositis (grade ≥ 2)	4/4	7/9
Bone pain (grade ≤ 2)	3/4	3/3
Increased hepatic transaminases (grade ≤ 2)	6/7	5/8
Increased hepatic transaminases (grade 3)	1/1	1/1
Median (range) number of transfusions		
Packed RBC transfusions	1 (0–4)	3 (0–6)
Platelet transfusions	0 (0–4)	0 (0–3)

Table 4

Serum granulocyte colony stimulating factor pharmacokinetic parameters [median (range)]

	Pegfilgrastim	Filgrastim
Number of patients	17	16
Dose (mcg)	6275 (4000–10000)	325 (100–480)
C _{max} (ng/mL)	65 (11–243)	12.7 (4.3–62.4)
T _{max} (h)	28.7 (4.7–146)	6 (3.8–8.3)
C _{ave} (ng/mL) *	20.2 (3.2–128)	6.5 (2.1–35.7)
CL/F (mL/hr/kg)	11.1 (2.1–152)	28.8 (6.5–93.2)

Abbreviations: C_{max}, peak concentration; T_{max}, time to peak concentration; C_{ave}, average concentration; CL/F, apparent clearance.

* C_{ave} = Area under concentration x time curve calculated to the last measured time point divided by the time of the last measured point for pegfilgrastim or to 24 h for filgrastim.