Pegfilgrastim on the Same Day Versus Next Day of Chemotherapy in Patients With Breast Cancer, Non–Small-Cell Lung Cancer, Ovarian Cancer, and Non-Hodgkin's Lymphoma: Results of Four Multicenter, Double-Blind, Randomized Phase II Studies

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Abstract

Purpose: To compare data on severe (grade 4) neutropenia duration and febrile neutropenia incidence in patients receiving chemotherapy with pegfilgrastim administered the same day or 24 hours after chemotherapy.

Patients and Methods: These were similar, randomized, double-blind phase II noninferiority studies of patients with lymphoma or non–small-cell lung (NSCLC), breast, or ovarian cancer. Each study was analyzed separately. The primary end point in each study was cycle-1 severe neutropenia duration. Approximately 90 patients per study were to be randomly assigned at a ratio of 1:1 to receive pegfilgrastim 6 mg once per cycle on the day of chemotherapy or the day after (with placebo on the alternate day).

Results: In four studies, 272 patients received chemotherapy and one or more doses of pegfilgrastim (133 same day, 139 next day). Three studies (breast, lymphoma, NSCLC) enrolled an adequate number of patients for analysis. However, in the NSCLC study, the neutropenic rate was lower than expected (only two patients per arm experienced grade 4 neutropenia). In the breast cancer study, the mean cycle-1 severe neutropenia duration was 1.2 days (95% confidence limit [CL], 0.7 to 1.6) longer in the same-day compared with the next-day group (mean, 2.6 *v* 1.4 days). In the lymphoma study, the mean cycle-1 severe neutropenia duration was 0.9 days (95% CL, 0.3 to 1.4) longer in the same-day compared with the next-day group (mean, 2.1 *v* 1.2 days). In the breast and lymphoma studies, the absolute neutrophil count profile for same-day patients was earlier, deeper, and longer compared with that for next-day patients, although the results indicate that same-day administration was statistically noninferior to next-day administration according to neutropenia duration.

Conclusion: For patients receiving pegfilgrastim with chemotherapy, pegfilgrastim administered 24 hours after chemotherapy completion is recommended.

Introduction

A major dose-limiting toxicity of chemotherapy is neutropenia. Infection resulting from neutropenia manifested as febrile neutropenia (FN) can lead to hospitalization, morbidity, and mortality in as many as 10% of patients.[1,2] Filgrastim is a recombinant growth factor that decreases the incidence, duration, and severity of neutropenia and minimizes infection—as manifested by FN[3,4]—by stimulating the proliferation, differentiation, and activation of the neutrophil lineage, thereby reducing neutrophil maturation time.[5] Neulasta (pegfilgrastim; Amgen, Thousand Oaks, CA), produced by covalently binding a 20-kd polyethylene glycol molecule to the *N*-terminus of filgrastim, represents an improvement over filgrastim. Compared with filgrastim, pegfilgrastim has a similar mechanism of action but a longer-acting effect, allowing patients to be injected only once per chemotherapy cycle compared with 10 to 11 days of filgrastim.[6,7] Pegfilgrastim is indicated to lower infection incidence, as manifested by FN, when administered once per cycle 24 hours after chemotherapy.[8]

Although millions of patients have received these growth factors, it is recognized that eliminating an office visit the day after chemotherapy would be desirable for patients, their families, and medical providers. Administration of filgrastim or pegfilgrastim within 24 hours before or after chemotherapy is not currently recommended because of the theoretical potential for increasing chemotherapy toxicity to myeloid progenitor cells after growth factor stimulation. Two studies observed a worsening in the incidence and/or duration of grade 4 neutropenia in patients receiving 5 consecutive days of overlapping fluorouracil or topotecan with filgrastim.[9,10] However, other studies have not reported increased myelosuppression when filgrastim was administered the day preceding, or concurrent with, cell-cycle–specific chemotherapies.[11-15] Interest in the same-day dosing schedule persists, highlighted recently in an article challenging the "24-hour mandate."[16]

To evaluate this dosing schedule, four tumor-specific studies were designed to assess the safety and efficacy of pegfilgrastim administered concurrently with chemotherapy. The malignancies chosen for evaluation—breast cancer, non-Hodgkin's lym-

Table 1. Key Study Information

Characteristic	Breast Cancer Study	NHL Study	NSCLC Study	Ovarian Cancer Study
Chemotherapy	Docetaxel 75 mg/m^2; doxorubicin 50 mg/m^2; cyclophosphamide 500 mg/m^2	Rituximab 375 mg/m^2; cyclophosphamide 750 mg/m^2; doxorubicin 50 mg/m^2; vincristine 1.4 mg/m^2; prednisone 100 mg (days 1-5)	Carboplatin AUC 6; docetaxel 75 mg/m^2	Topotecan 1.5 mg/m^2 administered days 1-5 of each cycle
Randomization stratification	Stage II or III *v* stage IV	Mantle-cell *v* diffuse large B-cell lymphoma	None	One *v* two prior chemotherapy regimens for ovarian cancer
No. of sites	14	24	22	10
Eligibility criteria				
Disease and stage	Diagnostically confirmed stage IV or histologically confirmed stage II or III breast cancer	Histologically proven mantle-cell lymphoma or diffuse large B-cell NHL (using REAL classification), Ann Arbor stage II, III, or IV	Histologically or cytologically confirmed stage IIIb (with pleural effusion) or stage IV NSCLC	Histologically confirmed primary peritoneal, epithelial, or tubal ovarian cancer relapsed after, or refractory to, one or two prior regimens
Performance status	ECOG 0 to 2	ECOG 0 to 2	ECOG 0 to 2	GOG 0 to 2
Prior chemotherapy	Stage II or III: untreated Stage IV: prior anthracycline ≤ 300 mg/m^2 and ≥ 30 days since anthracycline or herceptin	None allowed	None allowed	No prior topotecan

Abbreviations: NHL, non-Hodgkin's lymphoma; NSCLC, non–small-cell lung cancer; AUC, area under the curve; REAL, Revised European American Lymphoma Classification; ECOG, Eastern Cooperative Oncology Group; GOG, Gynecologic Oncology Group.

phoma (NHL), non–small-cell lung cancer (NSCLC), and ovarian cancer—comprise 42% of cancer deaths.[17]

Patients and Methods

Patients

The institutional review boards of participating centers approved each protocol, and all patients gave written informed consent before any study-related procedures were performed. Study-specific eligibility criteria are summarized in Table 1. Patients were eligible to participate if they were age ≥ 18 years, had adequate renal and liver function, and provided written informed consent. Patients were excluded if they had developed an active infection requiring treatment with systemic anti-infectives within 72 hours of chemotherapy.

Study Drug

Fixed-dose pegfilgrastim 6 mg and placebo were prepared as identical prefilled syringes for subcutaneous injection.

Study Design

These were randomized, double-blind studies exploring the safety and efficacy of administering pegfilgrastim on the same day of or day after chemotherapy. Each patient received an injection on day 1 within 4 hours after completion of chemotherapy and again 24 hours (± 2 hours) after chemotherapy on day 2. Each patient was randomly assigned to receive either pegfilgrastim on day 1 and placebo on day 2 or placebo on day 1 and pegfilgrastim on day 2. Patients could receive up to six chemotherapy cycles every 3 weeks (Table 1).

As recommended by the Infectious Disease Society of America, anti-infective prophylaxis was not permitted because of emerging antibiotic resistance.[18] A complete blood count was collected on the final day of actual and/or scheduled chemotherapy and then weekly for each cycle. Additionally, for cycles 1 and 3 (breast and ovarian studies) or cycles 1 and 4 (NHL and NSCLC studies), a complete blood count was obtained daily from day 5 (or day 7 for the ovarian study) until the absolute neutrophil count (ANC) was ≥ 0.5×10^9/L. If the patient felt feverish, he or she recorded oral body temperature on a diary card. If the temperature was ≥ 38.0°C, a complete blood count was scheduled. Oral temperature was collected daily by the patient until the temperature dropped below 38.0°C.

For the breast cancer and lymphoma studies, which used more myelosuppressive regimens than the other studies, the original plan was to evaluate the feasibility of same-day administration of pegfilgrastim in two phases. In the first phase, the safety data monitoring committee (SDMC) would evaluate the safety of 16 patients with advanced disease who had completed four chemotherapy cycles. After safety was established in these patients, the second phase would allow enrollment of patients with early-stage disease. However, in the breast study, because of the difficulty in accruing patients with advanced disease, the plan was amended to allow early-stage patients to enroll after the first seven patients with advanced disease were enrolled. Likewise, the lymphoma study was amended after the first three patients were enrolled, removing the requirement that only patients with mantle-cell lymphoma could be enrolled. This study closed early after enrolling 77 of the planned 90 patients with lymphoma as a result of additional enrollment problems.

The ovarian study was closed early on the basis of internal evaluations supported by a gynecologic oncology advisory board and individual study investigators, including the principal investigator. The major reason leading to study closure was a change in medical practice away from multiday topotecan (days 1 to 5, every 3 weeks) to once-per-week topotecan, which did not require pegfilgrastim use. Only 21 of 90 planned patients were enrolled; therefore, analyses were limited to descrip-

tive summaries, with no testing for noninferiority. All key end points were analyzed; however, the analyses were reduced in scope. Protocol amendments were not required for the NSCLC study.

Objectives and End Points

The primary objective in each study was to provide data on the safety and efficacy of pegfilgrastim administered on the same day versus on the day after chemotherapy, as measured by the duration of grade 4 neutropenia in cycle 1, which was the primary end point in each study. Secondary end points included cycle-1 neutropenia incidence and FN incidence (fever $\geq 38.2°C$ and ANC $< 0.5 \times 10^9$/L) in all cycles. The safety profile was measured by reports of adverse events and changes in laboratory values.

Study Procedures

In each study, patients received chemotherapy every 3 weeks for up to six cycles. All patients were randomly assigned in a blinded manner in a 1:1 ratio to receive pegfilgrastim on the last chemotherapy day (within 4 hours after the last dose) or approximately 24 hours after the last dose. Those patients receiving pegfilgrastim on the last chemotherapy day received a placebo injection approximately 24 hours later, and alternatively, those receiving pegfilgrastim approximately 24 hours after the last chemotherapy dose received placebo on the last chemotherapy day. A health care provider administered the study drug injections. Patients, investigators, and site personnel were blinded to the day of pegfilgrastim treatment.

For each study, an external SDMC reviewed partially blinded safety data (including hematology, adverse events, and chemotherapy dose reductions and delays) at the planned interim analysis and on a monthly basis. The SDMC recommended continuing enrollment both after the planned interim analysis, conducted after 16 patients had the opportunity to complete three (or four) chemotherapy cycles, and during each regular by-study data review.

Statistical Analyses

Patients receiving at least one dose of study drug were included in the primary analysis set for the efficacy and safety analyses. Additionally, the primary end point was also evaluated using a per-protocol patient subset analysis, including all patients who met the entry criteria with postbaseline assessments.

The clinical hypothesis that was tested in each of the studies was that the safety and efficacy of pegfilgrastim would not be altered by administering it on the same day of chemotherapy, as demonstrated by a similar duration of grade 4 neutropenia in cycle 1. To demonstrate noninferiority between the same-day and next-day groups, the upper bound of the two-sided 95% confidence limit (CL) of the difference (same day minus next day) in grade 4 neutropenia in cycle 1 was required to be less than 2 days. The 2-day margin was based on data from a pivotal filgrastim study.[3] The difference in mean (placebo minus filgrastim) was 2.95 days (two-sided 95% CL, 2.36 to 3.54). On the basis of the assumption of equivalent efficacy between pegfilgrastim and filgrastim and using the lower bound of the aforementioned 95% CL, a 2-day margin was selected. Although the 2-day margin could be considered permissive given that the registrational pegfilgrastim trials mandated a 1-day noninferiority margin,[6,7] it was felt that the 2-day margin was sufficient for a preliminary assessment in these phase II proof-of-concept studies. The planned sample size for each study was 90 patients. With a sample size of 45 patients in each group in cycle 1, assuming a one-sided α of 0.025 and standard deviation of 2.0 days for duration of grade 4 neutropenia, there was a greater than 95% chance of concluding that the true difference in mean duration of grade 4 neutropenia was less than 2 days, if in fact

Table 2. Patient Disposition by Study

	Breast Cancer Study				NHL Study				NSCLC Study				Ovarian Cancer Study			
	Same Day		Next Day		Same Day		Next Day		Same Day		Next Day		Same Day		Next Day	
Patient Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. screened	98				98				106				21			
Randomly assigned	47		46		37		40		45		45		10		11	
Received chemotherapy	46		45		36		39		44		44		8		11	
Received study drug	45		45		36		39		44		44		8		11	
Completed study	33	73	37	82	26	72	31	79	19	43	20	45	3	38	1	9
Discontinued early	12	27	8	18	10	28	8	21	25	57	24	55	5	62	10	91
Disease progression	1	2	0	0	0	0	0	0	11	25	12	27	3	38	4	36
Administrative decision	5	11	3	7	2	6	3	8	2	5	2	5	0	0	1	9
Consent withdrawn	0	0	1	2	4	11	0	0	2	5	1	2	0	0	5	45
Adverse event	1	2	0	0	2	6	2	5	4	9	3	7	2	25	0	0
Death	0	0	0	0	0	0	1	3	3	7	2	5	0	0	0	0
Other*	5	11	4	9	2	6	2	5	3	7	4	10	0	0	0	0

Abbreviations: NHL, non-Hodgkin's lymphoma; NSCLC, non–small-cell lung cancer.
* Other reasons for discontinuing the study early included protocol-specified deviation, protocol-specified criteria, and other.

the true duration were equal in the two groups. No inferential testing was performed for the external SDMC reviews; therefore, no adjustments for multiplicity were made.

The randomization for each study was stratified by high-risk and low-risk patients and generated using permuted blocks by a statistician not involved with the studies (Table 2). Site personnel called an interactive voice-response system to obtain numbers for patients, which the pharmacist used to assign appropriate treatment.

Secondary end points were summarized descriptively; no formal statistical testing was planned. All randomly assigned patients who received chemotherapy and at least one study drug dose were included in both the primary and per-protocol analysis sets according to random assignment. All patients who received a study drug were included in the safety analyses according to the treatment actually received. Changes from baseline in laboratory values were summarized using descriptive statistics. Efficacy and safety analyses were also provided by the stratification factor in a descriptive manner.

Results

Patient Characteristics

Across the four studies, 279 patients at 74 clinical sites in the United States were enrolled from February 2003 to August 2005. Of these, 272 patients received chemotherapy and at least one study drug dose and were included in the primary analysis set (Table 2). Except for the ovarian study, more patients in the same-day treatment groups terminated participation in the studies early compared with the next-day groups (Table 2).

Across the studies, baseline demographics and patient characteristics were generally well balanced between the same-day and next-day groups (Table 3). Baseline imbalances between the groups were only observed in the NSCLC study, in which there were slightly more patients with stage IV disease in the next-day group (91%) compared with the same-day group (77%) and slightly more patients with Eastern Cooperative Oncology Group performance status of 0 in the same-day group (55%) compared with the next-day group (30%). There were no notable protocol deviations affecting the analysis or interpretation of the results for the primary end point in any of the studies.

Efficacy

In cycle 1 of the breast study, grade 4 neutropenia was reported among 93% of same-day patients and 78% of next-day patients (Table 4, Fig 1A). More patients had severe neutropenia duration of 3 days or longer in the same-day group (50%) than in the next-day group (18%). Mean severe neutropenia duration was 1.2 days (95% CL, 0.7 to 1.6) longer in the same-day group than in the next-day group (mean, 2.6 *v* 1.4 days). However, the results indicated the same-day group was statistically noninferior to the next-day group with respect to duration of severe neutropenia (ie, the upper bound of the 95% CL [1.6] was less than the 2-day margin). Similar between-arm differences were observed for subgroups of patients with stage II to III or IV

Table 3. Patient Demographics and Baseline Disease Characteristics by Study

Demographic or Characteristic	Breast Cancer Study				NHL Study*				NSCLC Study				Ovarian Cancer Study			
	Same Day		Next Day		Same Day		Next Day		Same Day		Next Day		Same Day		Next Day	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	45		45		36		39		44		44		8		11	
Female	45	100	45	100	22	61	25	64	12	27	18	41	8	100	11	100
Age, years																
Median	53		51		60		60		64		65		58		58	
Range	26		31		28		26		36		40		38		36	
	68		71		83		85		80		82		81		75	
Race																
White	40	89	35	78	27	75	29	74	35	80	41	93	7	88	9	82
Black	2	4	4	9	5	14	2	5	7	16	3	7	0	0	1	9
Other†	3	7	6	13	4	11	8	21	2	5	0	0	1	13	1	9
Disease stage																
II	33	73	25	56	11	31	10	26	—		—		§		§	
III‡	5	11	11	24	13	36	16	41	10	23	4	9	—		—	
IV	7	16	9	20	12	33	13	33	34	77	40	91	—		—	
Baseline ANC, $\times 10^9$/L																
Mean	8.6		9.1		5.5		6.2		12.9		13.0		4.4		4.3	
SD	4.61		5.20		2.28		3.40		5.76		6.03		1.96		1.12	

Abbreviations: NHL, non-Hodgkin's lymphoma; NSCLC, non–small-cell lung cancer; ANC, absolute neutrophil count; SD, standard deviation.
* Eight patients (same day, three; next day, five) enrolled with mantle-cell lymphoma; the remainder had diffuse large B-cell lymphoma.
† Other races included Asian, Hispanic, Lebanese, and Filipino.
‡ For the NSCLC study, disease stage III represents patients with disease stage IIIb and pleural effusion.
§ Relapsed: same day, seven patients (88%); next day, six patients (55%).

Table 4. Summary of Neutropenia by Study

	Breast Cancer Study				NHL Study				NSCLC Study				Ovarian Cancer Study			
	Same Day		Next Day		Same Day		Next Day		Same Day		Next Day		Same Day		Next Day	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	45		45		36		39		44		44		8		11	
Grade 4 neutropenia*																
Cycle 1 incidence	42	93	35	78	31	86	25	64	2	5	2	5	6	75	6	55
Duration, days																
0	3	7	10	22	4	11	14	36	40	91	40	91	2	25	5	46
1	3	7	16	36	7	19	10	26	2	5	2	5	2	25	1	9
2	16	36	11	24	11	31	9	23					1	13	1	9
≥ 3	23	50	8	18	13	36	6	15					3	38	4	36
Unknown					2	5†	2	5†								
Mean duration, days	2.6		1.4		2.1		1.2		0.05		0.05		1.9		2.4	
95% CL	2.2 to 2.9		1.1 to 1.7		1.7 to 2.5		0.8 to 1.6		−0.02 to 0.1		−0.02 to 0.1		0.4 to 3.3		0.5 to 4.3	
Mean difference‡	1.2				0.9				Not calculated				Not calculated			
95% CL	0.7 to 1.6				0.29 to 1.42											
Cycle 1 ANC nadir, $\times 10^9$/L																
Geometric mean§	0.06		1.8		0.08		0.30		3.33		3.23		Not calculated			
95% CL	0.04 to 0.09		0.12 to 0.28		0.05 to 0.12		0.18 to 0.50		2.52 to 4.39		2.33 to 4.48					
Febrile neutropenia‖																
Cycle 1	10	22	3	7	4	11	1	3	0	0	0	0	1	13	2	18
Overall	15	33	5	11	6	17	6	15	0	0	0	0	1	13	2	18

Abbreviations: NHL, non-Hodgkin's lymphoma; NSCLC, non–small-cell lung cancer; CL, confidence limit; ANC, absolute neutrophil count.
* Grade 4 neutropenia is defined as ANC $< 0.5 \times 10^9$/L.
† Could not assess neutropenia duration because of inadequate ANC values.
‡ Treatment difference = same day − next day.
§ Because of the distribution of ANC nadir data, geometric mean is more representative than arithmetic mean for this comparison.
‖ Febrile neutropenia: temperature ≥ 38.2°C and ANC $< 0.5. \times 10^9$/L on same or next day.

disease (data not shown). Across all cycles, the FN incidence was 33% for same-day patients and 11% for next-day patients, with most patients experiencing FN in cycle 1. Similar trends were observed in cycle 3 (data not shown).

In cycle 1 of the lymphoma study, grade 4 neutropenia was reported among 86% of same-day patients and 64% of next-day patients (Table 4, Fig 1B). More patients had severe neutropenia duration of 3 days or longer in the same-day group (36%) than in the next-day group (15%). Mean severe neutropenia duration was 0.9 days (95% CL, 0.3 to 1.4) longer in the same-day group than in the next-day group (mean, 2.1 *v* 1.2 days). However, the results indicated the same-day group was statistically noninferior to the next-day group with respect to duration of severe neutropenia (ie, the upper bound of the 95% CL [1.4] was less than the 2-day margin). In cycle 1, FN was 11% for the same-day patients and 3% for the next-day patients, whereas across all cycles, FN incidence was 17% and 15%, respectively. Similar trends were observed in cycle 3 (data not shown).

In cycle 1 of the NSCLC study, only two patients (5%) in each group experienced grade 4 neutropenia for a duration of 1 day each (Table 4, Fig 1C). Because more than 90% of patients did not experience grade 4 neutropenia, and there were no FN episodes in either group during the study, the difference in mean between the groups was not calculated. For the ovarian study, descriptive analyses are presented (Table 4, Fig 1D), although no conclusions could be drawn.

Clinical Adverse Events

In general, serious adverse events experienced by patients in each of these studies were those expected for patients with malignancies receiving myelosuppressive chemotherapy. No patient experienced bone pain that was considered serious in any study. In the breast, NSCLC, and ovarian studies, no serious adverse events were considered by the investigators to be study-drug related.

In the breast study, 24% and 11% of patients in the same-day and next-day groups, respectively, reported serious adverse events. The most commonly reported serious adverse event was FN (same day, 18%; next day, 4%).

In the lymphoma study, 33% of patients in both the same-day and next-day groups reported serious adverse events. More pyrexia and gastrointestinal disorders were experienced by patients in the next-day group than in the same-day group. Four patients experienced serious adverse events that were reported as study-drug related, including one same-day patient (myocardial infarction and congestive cardiac failure in a 75-year-old man) and three next-day patients (allergic alveolitis, FN and pulmo-

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