



## Pegfilgrastim support for full delivery of BEACOPP-14 chemotherapy for patients with high-risk Hodgkin's lymphoma: results of a phase II study

Andreas Engert  
Henning Breidenfeld  
Hartmut Döhner  
Anthony D. Ho  
Norbert Schmitz  
Dietmar Berger  
Pamela Bacon  
Tomas Skacel  
Valerie Easton  
Volker Diehl

The primary endpoint of this feasibility study was to determine whether pegfilgrastim support could enable the delivery of the full dose of BEACOPP chemotherapy every 14 days on schedule. Forty-one patients with high-risk Hodgkin's lymphoma were randomized to receive pegfilgrastim (6 mg) on day 4 or 8 of each cycle. Eighty-one percent of cycles administered were delivered at full dose and on schedule (FDOS). Response was retrospectively assessed in 27 patients at 6 months; 23 of these 27 patients (85%) achieved a complete response and one (4%) achieved a partial response. Toxicities were mostly moderate in intensity. These results support the feasibility of delivering full dose, on schedule BEACOPP-14, chemotherapy with pegfilgrastim support.

Key words: Hodgkin's lymphoma, chemotherapy, phase I.

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From the Department I of Internal Medicine, University of Cologne, Cologne, Germany (AE, HB, VD); Internal Medicine III, University of Ulm, Ulm, Germany (HD); Hematology and Oncology, University of Heidelberg, Heidelberg, Germany (ADH); Hematology, St. Georg General Hospital, Hamburg, Germany (NS); Amgen (Europe) GmbH, Zug, Switzerland (DB, PB, TS); Amgen Ltd, Cambridge, United Kingdom (VE).

### Correspondence:

Andreas Engert, M.D., University Hospital of Cologne, Department of Internal Medicine I, Kerpener Str. 62, D-50924 Köln, Germany. E-mail address: a.engert@uni-koeln.de

Although most patients with Hodgkin's lymphomas (HD) respond to first-line chemotherapy,<sup>1</sup> 20% of patients with aggressive disease require more intensive regimens<sup>2,3</sup> that are associated with a higher incidence of neutropenia contributing to infection, morbidity, mortality, and chemotherapy dose modifications. Granulocyte colony-stimulating factors (G-CSF), administered for hematopoietic support, decrease the incidence of severe neutropenia and have been demonstrated to render full and on-time dosing more feasible.<sup>5-11</sup>

In patients with high-risk HD, it was shown that BEACOPP chemotherapy, with filgrastim support, improved survival rates compared to those produced by COPP/ABVD treatment.<sup>16</sup> Subsequent increased-dose and dose-dense studies found that BEACOPP administered in 14-day cycles (BEACOPP-14) resulted in complete response rates of 94% and, compared with BEACOPP-escalated, less toxicity thus warranting further evaluation.<sup>12-15</sup>

Pegfilgrastim has been demonstrated to be not inferior to filgrastim<sup>10,17</sup> in terms of efficacy, with the advantages of single dose administration and neutrophil-mediated clearance.<sup>18</sup> This prospective study was designed to assess the feasibility of delivering BEACOPP-14 chemotherapy at a full dose and on schedule (FDOS) to high-risk HD patients, with pegfilgrastim support administered as a single 6 mg dose on day 4 or 8 of each cycle.

## Design and Methods

### Patients

Forty-one high-risk HD patients, aged 18-60 years, were enrolled at eight centers in

Germany between August 2001 and January 2004 with histologically confirmed disease in stages IIB, IIIA, IIIB, or IV. The usual inclusion and exclusion criteria applied.<sup>15</sup> Exclusionary laboratory parameters included white cell count  $<2 \times 10^9/L$ , platelets  $<100 \times 10^9/L$ , creatinine clearance  $<60$  mL/min, bilirubin  $>2$  mg/dL, aspartate or alanine transferase  $>100U/L$ . Written informed consent was obtained from all patients.

### Study design and statistical analysis

Patients received adriamycin 25 mg/m<sup>2</sup> IV on day 1, cyclophosphamide 650 mg/m<sup>2</sup> IV on day 1, etoposide 100 mg/m<sup>2</sup> (or etoposide phosphate 113 mg/m<sup>2</sup>) on days 1-3, procarbazine 100 mg/m<sup>2</sup> PO on days 1-7, prednisone 80 mg/m<sup>2</sup> PO on days 1-7, bleomycin 10 mg/m<sup>2</sup> IV on day 8, and vincristine 1.4 mg/m<sup>2</sup> IV (maximum 2 mg) on day 8, administered every 14 days [BEACOPP-14] for up to eight cycles.<sup>15</sup> Patients were randomly assigned (1:1) to receive a 6 mg subcutaneous dose of pegfilgrastim on day 4 or 8 of each cycle. The primary endpoint was to determine the proportion of cycles given at planned FDOS, and the proportion of patients receiving FDOS chemotherapy. *On schedule* cycles began  $\leq 17$  days after the start of the previous cycle, and *full dose* cycles delivered  $>75\%$  of each agent (excluding prednisone, vincristine and bleomycin). Secondary aims of the study were to evaluate the incidence of severe neutropenia (defined as an absolute neutrophil count  $<0.5 \times 10^9/L$ ), response rates, and the safety profile. The study was not powered to make formal comparisons between study arms. Two-sided 95% confidence intervals were used to describe variations in the study's end-points. The number

**Table 1.** Patients' demographics and baseline characteristics.

Characteristic	Pegfilgrastim, 6 mg SC		
	Day 4 (n=21)	Day 8 (n=20)	Total (n=41)
Sex			
Male	11 (52%)	13 (65%)	24 (59%)
Female	10 (48%)	7 (35%)	17 (41%)
Age			
Mean (range)	31.6 (18-58)	33.6 (18-59)	32.6 (18-59)
Baseline ANC (×10 <sup>6</sup> /L)			
Mean (SD)	8.97 (5.20)	7.19 (3.28)	8.10 (4.41)
Disease stage			
IIB	5 (24%)	2 (10%)	7 (17%)
IIIA/IIIB	3 (14%)/7(33%)	8 (40%)/5(25%)	11(27%)/12(29%)
IVA/IVB	4 (19%)/2(10%)	3 (15%)/2(10%)	7(17%)/4(10%)
Histological subtype			
Classic Hodgkin's lymphoma	4(19%)	1 (5%)	5 (12%)
Nodular sclerosis grade 1	6(29%)	6 (30%)	12 (29%)
Nodular sclerosis grade 2	1(5%)	2 (10%)	3 (7%)
Mixed cellularity	4(19%)	5 (25%)	9 (22%)
Lymphocyte rich	3(14%)	2 (10%)	5 (12%)
Lymphocyte predominant lymphoma	1(5%)	1 (5%)	2 (5%)
Unclassified	2 (10%)	3 (15%)	5 (12%)
ECOG Performance Status			
0-fully active	15 (71%)	13 (65%)	28 (68%)
1-symptoms but ambulatory	5 (24%)	6 (30%)	11 (27%)
2-in bed < 50% of time	1 (5%)	0 (0%)	1 (2%)
Unknown	0 (0%)	1 (5%)	1 (2%)

and proportion of cycles in which FDOS chemotherapy was administered were recorded. The number and proportion of patients receiving FDOS chemotherapy were recorded over all cycles, and by cycle. Reasons for dose delays were summarized by cycle.

### Study assessments

Samples for complete blood counts were drawn on day 1 prior to chemotherapy, on day 3, and then three times weekly on or after day 8 until day 14. Additional blood samples were collected on day 1 for chemistry analyses. Treatment safety was assessed from the incidence of adverse events, including febrile neutropenia, absolute neutrophil counts (ANC), changes in laboratory parameters, and concomitant use of medication.

### Response criteria

Initial disease staging (confirmed by a central diagnostic panel) was performed at screening. The patients were restaged and response assessed after cycle 4, at the end of the treatment, and approximately 6 months after the end of the study (via retrospective analysis).

## Results and Discussion

### Patient's characteristics

Forty-one patients were enrolled and randomly

**Table 2.** Patients' disposition and summary of cycles administered at full-dose and on-schedule and patients receiving the full dose of chemotherapy on schedule.

	Pegfilgrastim, 6 mg SC		
	Day 4 (n=21)	Day 8 (n=20)	Total (n=41)
Patients received pegfilgrastim	21 (100%)	20 (100%)	41 (100%)
Patients' disposition			
Completed study (8 cycles)	17 (81%)	17 (85%)	34 (83%)
Ineligible	2 (10%)	2 (10%)	4(10%)
Discontinued study due to adverse event	1 (5%)	1 (5%)	2(5%)
Death on study	1 (5%)	0 (0%)	1 (2%)
Summary of cycles*			
Number of cycles planned	168	160	328
Number of cycles administered	151 (90%)	143 (89%)	294 (90%)
Number of cycles administered at FDOS <sup>o</sup>	122 (81%)	116 (81%)	238 (81%)
95% CI for proportion of cycles administered at FDOS	74%-87%	74-87%	
Number of patients receiving FDOS chemotherapy <sup>a</sup>			
All cycles	5 (29%)	5 (29%)	10 (29%)
Delay in any cycle only	8 (47%)	9 (53%)	17 (50%)
Dose reduction in any cycle only	1 (6%)	1 (6%)	2 (6%)
Both delay and reduction in any cycle	3 (18%)	2 (12%)	5 (15%)
95% CI for proportion of patients receiving FDOS chemotherapy	10%-56%	10%-56%	

FDOS: full-dose, on-schedule; >75% of the protocol-specified dose for specified agents in the chemotherapy regimen and a delay of ≤3 days; CI: confidence interval; <sup>a</sup> based on patients receiving pegfilgrastim; <sup>o</sup> based on number of cycles administered; <sup>b</sup> based on number of patients who completed the study (8 cycles).

assigned to receive pegfilgrastim on day 4 (n=21) or day 8 (n=20). At baseline, the treatment groups were well matched (Table 1). Thirty-four patients (83%) received all eight cycles of chemotherapy and 27 completed the follow-up. During the follow-up period, 15 patients (56%) received radiotherapy. The patients' management is shown in Table 2.

### Efficacy

All patients in the analysis set received at least one dose of pegfilgrastim (Table 2). Overall, 294(90%) of 328 planned cycles were administered; 81% at FDOS. Of the 34 patients who received all eight cycles of chemotherapy 10 (29%) received all cycles at the FDOS. The most common reasons for not receiving FDOS chemotherapy were low ANC and low platelet counts.

More patients who received pegfilgrastim on day 8 experienced severe neutropenia [15 patients, 75%; 95% CI (56%, 94%)], compared to patients given the G-CSF on day 4 [9 patients, 43%; 95% CI (22%, 64%)]. Response rates were 85% at the end of study, and 89% at follow-up, with 23 (85%), and one (4%) patients achieving complete and partial remission, respectively. Twelve (92%) patients given pegfilgrastim on day 4 versus 11 (79%) of those treated on day 8 achieved complete responses (Table 3).

**Table 3.** Incidence of grade 3 and 4 hematologic toxicities and summary of disease response.

Characteristic	Pegfilgrastim, 6 mg SC		
	Day 4 (n=21)	Day 8 (n=20)	Total (n=41)
<b>White blood cells</b>			
Grade 3 (< 2.0-1.0×10 <sup>9</sup> /L)	5 (24%)	2 (10%)	7 (17%)
Grade 4 (< 1.0×10 <sup>9</sup> /L)	10 (48%)	16 (80%)	26 (63%)
<b>Absolute neutrophil count</b>			
Grade 3 (< 1.0-0.5×10 <sup>9</sup> /L)	5 (24%)	2 (10%)	7 (17%)
Grade 4 (< 0.5×10 <sup>9</sup> /L)	9 (43%)	15 (75%)	24 (59%)
<b>Platelets</b>			
Grade 3 (< 50.0-25.0×10 <sup>9</sup> /L)	2 (10%)	4 (20%)	6 (15%)
Grade 4 (< 25.0×10 <sup>9</sup> /L)	4 (19%)	3 (15%)	7 (17%)
<b>Hemoglobin</b>			
Grade 3 (< 80-65 g/L)	12 (57%)	10 (50%)	22 (54%)
Grade 4 (< 65 g/L)	3 (14%)	5 (25%)	8 (20%)
<b>Patients' response at follow-up (n=13)</b>			
Complete remission	12 (92%)	11 (79%)	23 (85%)
Partial remission	0 (0%)	1 (7%)	1 (4%)
Progressive disease	0 (0%)	1 (7%)	1 (4%)
Not available	1 (8%)	1 (7%)	2 (7%)

Grade 3 and 4 toxicities are defined according to the Common Terminology Criteria for Adverse Events, v. 3.0 (CTCAE). For patients who experienced both grade 3 and 4 toxicities, only the worst occurrence (grade 4) was counted. Percentages are based on the number of patients in the subset.

## Safety

The most commonly recorded mild or moderate adverse events were anemia, fever, fatigue, and skeletal pain. Treatment-related adverse events (>1 occurrence) were skeletal, back, and pelvic pain, occurring in 17 (42%), 7 (17%), and 3 (7%) patients, respectively. The incidence of grade 3/4 hematologic toxicities is present-

ed in Table 3. Eight patients (four patients in each group), reported 11 episodes of febrile neutropenia none resulting in withdrawal from the study. Severe non-hematologic toxicities occurred in 25 (61%) patients. Related events (>1 occurrence) were skeletal pain [6 (14%)] and pelvic pain [3 (7%)]. Skeletal pain resulted in one patient's removal from the study and another patient was hospitalized, without treatment delay, for back pain. One death, not related to the treatment, occurred during the study.

BEACOPP-14 chemotherapy with filgrastim support has been demonstrated to be a well-tolerated and effective regimen.<sup>15</sup> In the present study, pegfilgrastim supported the on-schedule delivery of 81% of BEACOPP-14 cycles, and was comparable to results reported by the German Hodgkin's Study Group for number of patients completing eight cycles (83% versus 91%) and complete response rates (85% versus 94%).

Results observed in each treatment arm were broadly comparable. Fever occurred twice as often in the patients given pegfilgrastim on day 4 but this group had a lower incidence of severe neutropenia. This may be attributable to the earlier pegfilgrastim delivery, as the ANC nadir occurs around day 8. Early pegfilgrastim treatment may also provide an anti-inflammatory environment for chemotherapy, thus enhancing more stable neutrophil populations.<sup>18</sup>

The results of the study reported here support the feasibility of delivering BEACOPP-14 at FDOS with pegfilgrastim administration on either study day. However, the lower rate of severe neutropenia in the group receiving the G-CSF on day 4 may indicate a potential benefit from administering pegfilgrastim earlier in the cycle, and warrants further study.

AE: conception of writing the study, principle investigator; HB: treatment of patients, conception of the study; HD, ADH, NS: treatment of patients, conception of the study; DB: conception, financial support; PB: conception and conduction of the study, writing committee; TS: conception and conduction of the study, writing committee; VD: conception of the study, writing committee.

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