Randomized comparison of pegfilgrastim day 4 versus day 2 for the prevention of chemotherapy-induced leukocytopenia

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Received 12 June 2010; revised 20 August 2010; accepted 21 October 2010

Background: To study the effects of deferring pegfilgrastim until day 4 on the reduction of chemotherapy-induced leukocytopenia.

Patients and methods: Patients of age 61–80 years with aggressive lymphoma were randomly assigned to receive 6 mg pegfilgrastim on day 2 or 4 of a 2-week chemotherapy regimen (R-CHOP-14).

Results: Two hundred and ninety-two and 313 chemotherapy cycles were evaluable in 103 patients. Post-nadir pegfilgrastim serum levels were higher after day 4 than after day 2 application. This was associated with an attenuated leukocyte nadir after day 4 pegfilgrastim and there were fewer days with leukocytes <2·10^3/mm^3 compared with day 2 pegfilgrastim. Grade 3 and 4 leukocytopenias (70% versus 43.3%; P<0.001) and grade 4-only leukocytopenias (47% versus 20.5%; P<0.001) were more frequent after day 2 pegfilgrastim. There were more chemotherapy cycles with grade 3 and 4 infections after day 2 than day 4 pegfilgrastim (9.4% versus 6.0%; P=0.118). Interventional antibiotics were given more often after day 2 than after day 4 pegfilgrastim (30.7% versus 21.9% of cycles; P=0.008).

There were five deaths during leukocytopenia after day 2 and none after day 4 pegfilgrastim (P=0.027).

Conclusions: Administration of pegfilgrastim on day 4 was more effective in reducing severe leukocytopenias and resulted in fewer deaths during leukocytopenia. Pegfilgrastim should be given on day 4 to better exploit its myeloprotective potential.

Key words: chemotherapy, infections, leukocytopenia, pegfilgrastim, therapy-associated deaths

introduction

Prophylactic use of myeloid growth factors reduces the severity and duration of neutropenia in patients receiving myelosuppressive chemotherapy. Several studies [1–5] in a wide spectrum of chemotherapy regimens for solid tumors [3, 4] or lymphomas [6, 7] established that the pegylated granulocyte colony-stimulating factor (G-CSF) pegfilgrastim, which is a long-acting form of filgrastim, can be administered as a single dose per cycle and is clinically equivalent to filgrastim, which has to be administered daily for up to 10 days after the myelosuppressive drug. Pegfilgrastim has the same mechanisms of action as the first-generation filgrastim, but has markedly reduced renal clearance, with neutrophil-mediated clearance being the major route of elimination. As a result, clearance of pegfilgrastim is decreased, and serum concentrations are sustained throughout the duration of neutropenia [8], but serum concentrations fall rapidly below the therapeutic threshold with recovery of the neutrophil counts in the peripheral blood. Since neutrophil-mediated clearance of pegfilgrastim is operative both before and after neutropenia, we wondered whether deferring the administration of pegfilgrastim until neutrophil counts start dropping after chemotherapy might result in a better exploitation of pegfilgrastim’s myeloprotective potential.

patients and methods

patients

The study was conducted in accordance with the Helsinki declaration. The protocol was approved by the ethical review committee of each
participants' informed consent. Eligibility and exclusion criteria were identical to those applied in the RICOVER-60 study of the DSHNHL (Deutsche Studiengruppe für Hochmaligne Non-Hodgkin Lymphome) [9]. Patients were eligible if they had previously untreated biopsy-confirmed aggressive non-Hodgkin’s lymphoma of the B-cell type according to the Revised European-American Lymphoma Classification [10] (translated into the World Health Organization (WHO) classification [11]) and were between 61 and 80 years. Patients with the acquired immunodeficiency syndrome; marked impairment of cardiac, pulmonary, hepatic or renal function; WHO performance status of four; initial white blood cell (WBC) < 2.5 × 10^9/l; initial platelet < 100 × 10^9/l or inability to comply with study requirements were excluded. The patients had mandatory baseline examinations including physical examination, laboratory tests, computed tomography of chest and abdomen and a bone marrow biopsy. Prophylactic levofloxacin 500 mg/day [12] was recommended starting from day 7 of a chemotherapy cycle until recovery.

study design
After prephase treatment that consisted of a single administration of 1 mg vincristine and 100 mg prednisone for 7 days, patients were randomly assigned to receive six or eight cycles of 2-week CHOP-14 (cyclophosphamide, vincristine, doxorubicin, prednisone) with or without eight applications of rituximab. In contrast to the RICOVER-60 study where patients were to receive pegfilgrastim or lenograstim starting on day 4 of the CHOP-14 regimen, patients in this open-label trial had a second randomization to receive pegfilgrastim 6 mg s.c. either on day 2 or on day 4 of each CHOP-14 cycle. The randomization into the two pegfilgrastim schedules was carried out at a 1:1 ratio using the minimization algorithm by Pocock [13] after stratification for centers, elevated lactate dehydrogenase, advanced stage III/IV, performance status [Eastern Cooperative Oncology Group (ECOG) 0,1 versus ECOG 2, 3], age > 70 and bulky disease. The trial was planned as a randomized phase II trial with several primary end points related to myelotoxicity, safety, and adherence to chemotherapy. Efficacy end points were secondary. We did not carry out a blinded study because the end points of the study were objectively measurable parameters and not subject to subjective assessment. The trial was designed to provide adequately precise estimators and confidence limits for time course of leukocytes, myelotoxicity, frequency of infections, days with antibiotics, days in hospital, estimators for the time interval between successive treatment cycles and estimators for dose erosion. Based on data from the previous NHL-B-trial [14], the necessary case number deemed to cover all these requirements was 52 patients in each arm (104 in total).

Overall, a median of two measurements per cycle and patient was reported. Using the pooled data from all measurements, we identified time windows for the nadir values: days 10–12 for thrombocytopenia and days 8–10 for the leukocytes in the context of pegfilgrastim support. The lowest WBC counts within this time window were transformed into an NCI (National Cancer Institute)—Common Toxicity Criteria (CTC) grade. Cycles were only considered evaluable if cell count data were available from the nadir time windows. With respect to anemia, the lowest hemoglobin value available per cycle was used to code the toxicity grade. Early terminations of the chemotherapy because of insufficient response were censored at the time of termination. Treatment duration, dose intensity and dose erosion were estimated according to Kaplan–Meier as described elsewhere [15].

Characteristics of patients, toxic effects according to the NCI–CTC criteria (version 2) and therapeutic interventions were compared by χ² tests and, if necessary, by Fisher’s exact tests. Serum levels, age and body surface area (BSA) were compared by Mann–Whitney tests.

results
From May 2004 to July 2005, 109 patients were recruited from 34 institutions not participating in the synchronously conducted RICOVER-60 study [9]. Signed informed consent was missing from 6 patients leaving 103 patients assessable (Figure 1), of whom 51 were randomly assigned to receive pegfilgrastim on day 2, and 52 on day 4, respectively. This included the last 18 patients who were randomly assigned to receive pegfilgrastim day 2 or day 4, respectively, but were no longer randomized into the different chemotherapy arms because in the meantime, the RICOVER-60 study (which was conducted in parallel in centers of the DSHNHL not participating in this pegfilgrastim trial) had been stopped because of the superiority of the arm with six cycles of CHOP and eight administrations of rituximab. Of these 18 patients, 6 were switched to 6× R-CHOP-14 (rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone) when already under therapy, while the last 12 patients were directly assigned to receive six cycles of CHOP-14 and eight applications of rituximab. The analysis was carried out on an intention-to-treat principle including all patients randomized. A median of two measurements of hemoglobin, leukocyte and platelet counts was determined per chemotherapy cycle per patient. There were more female patients assigned to pegfilgrastim day 2 than day 4 (63% versus 46%; P = 0.09) and median BSA was slightly lower in the pegfilgrastim day 2 group (1.8 versus 1.9 m²; P = 0.107), but otherwise arms were well balanced with respect to known risk factors (Table 1).

pegfilgrastim serum levels
Pegfilgrastim serum levels were measured on day 1 of the next chemotherapy cycle in 12 cycles in patients assigned to day 2 pegfilgrastim and in 20 chemotherapy cycles in patients assigned to day 4 pegfilgrastim. As shown in Figure 2, post-nadir serum levels were higher in the pegfilgrastim day 2 samples (median: 0.58 ng/ml; range 0.15–1.27) compared with the pegfilgrastim day 2 samples (0.12 ng/ml; range 0.0–0.2; P < 0.001).

hematological parameters
The assessable 103 patients received 605 cycles with pegfilgrastim (292 in day 2 and 313 in day 4 pegfilgrastim) and chemotherapy; eight cycles were not evaluable because no blood counts were documented during the nadir window, leaving 597 cycles. In 92% of the cycles in the day 2 and in 94% in the day 4 arm, pegfilgrastim was given on the assigned day. The median maximum leukocyte count after day 2 pegfilgrastim was higher than after day 4 pegfilgrastim (43 versus 30 × 10^9/mm³; Figure 3A). However, the nadir after day 2 pegfilgrastim was lower (median 1 versus 2.4 × 10^9/mm³ on day 8; 0.95 versus 1.9 × 10^9/mm³ on day 9 and 1.8 versus 2.4 × 10^9/mm³ on day 10) and there were more days with leukocytes <2 × 10^9/mm³ (grade 3 and 4) after day 2 pegfilgrastim compared with day 4 pegfilgrastim (3 versus 0 days). This favorable effect of day 4 application of pegfilgrastim on the course of leukocyte counts was observed both in male and female patients (Figure 3B and C). After day 2 pegfilgrastim, more chemotherapy cycles with grade 3 and 4 leukocytopenias (70% versus 43.3%; P < 0.001) and grade 4 leukocytopenias only (47% versus 20.5%; P < 0.001) occurred. This was observed independently of the assignment to treatment with or without rituximab (rituximab...
arms: cycles with grade 3 and 4 leukocytopenias 72.3% versus 48.1%, \( P = 0.014 \); non-rituximab arms: cycles with grade 3 and 4 leukocytopenias 67.9% versus 39.7%, \( P = 0.002 \) or the number of chemotherapy cycles (6x CHOP: cycles with grade 3 and 4 leukocytopenias 70.9% versus 31.9%, \( P < 0.001 \); 8x CHOP: cycles with grade 3 and 4 leukocytopenias 68.9% versus 58.2%, \( P = 0.270 \)). On a per-patient basis, there were more patients who experienced at least one cycle of chemotherapy with grade 3 and 4 leukocytopenia (84.4% versus 70.3%; \( P = 0.166 \)) or grade 4 leukocytopenia only (65.6% versus 43.2%; \( P = 0.063 \)) after day 2 than after day 4 pegfilgrastim (Table 2). There were no differences with respect to anemias or thrombocytopenias.

### Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>6x CHOP, Peg day 2</th>
<th>6x CHOP, Peg day 4</th>
<th>6x R-CHOP, Peg day 2</th>
<th>6x R-CHOP, Peg day 4</th>
<th>8x CHOP, Peg day 2</th>
<th>8x CHOP, Peg day 4</th>
<th>8x R-CHOP, Peg day 2</th>
<th>8x R-CHOP, Peg day 4</th>
<th>( P ) value</th>
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<tbody>
<tr>
<td>Age, median</td>
<td>70.5 (63–77)</td>
<td>69 (61–76)</td>
<td>67 (59–77)</td>
<td>68 (61–80)</td>
<td>69 (61–76)</td>
<td>69 (62–77)</td>
<td>68 (61–80)</td>
<td>70 (61–78)</td>
<td>0.829</td>
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<td>(range)</td>
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<td>Male, ( n ) (%)</td>
<td>2 (16.7)</td>
<td>4 (33.3)</td>
<td>8 (47.1)</td>
<td>10 (58.8)</td>
<td>7 (63.6)</td>
<td>6 (50.0)</td>
<td>2 (18.2)</td>
<td>8 (72.7)</td>
<td>0.049</td>
</tr>
<tr>
<td>Female, ( n ) (%)</td>
<td>10 (83.3)</td>
<td>8 (66.7)</td>
<td>9 (52.9)</td>
<td>7 (41.2)</td>
<td>4 (36.4)</td>
<td>6 (50.0)</td>
<td>9 (81.8)</td>
<td>3 (27.3)</td>
<td></td>
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<tr>
<td>BSA cycle 1: median</td>
<td>1.7 (1.7/1.9)</td>
<td>1.8 (1.7/2.1)</td>
<td>1.8 (1.6/2.1)</td>
<td>1.9 (1.7/2.1)</td>
<td>1.9 (1.8/2.0)</td>
<td>1.9 (1.7/2.1)</td>
<td>1.7 (1.7/1.8)</td>
<td>1.9 (1.7/2.0)</td>
<td>0.161</td>
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<td>(lower/upper quartile)</td>
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<tr>
<td>LDH &gt; UNV, ( n ) (%)</td>
<td>7 (58.3)</td>
<td>6 (50.0)</td>
<td>11 (64.7)</td>
<td>11 (64.7)</td>
<td>7 (63.6)</td>
<td>7 (58.3)</td>
<td>6 (54.5)</td>
<td>6 (59.2)</td>
<td>0.992</td>
</tr>
<tr>
<td>ECOG &gt; 1, ( n ) (%)</td>
<td>3 (25.0)</td>
<td>2 (16.7)</td>
<td>4 (23.5)</td>
<td>3 (17.6)</td>
<td>1 (9.1)</td>
<td>3 (25.0)</td>
<td>2 (18.2)</td>
<td>1 (9.1)</td>
<td>0.942</td>
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<tr>
<td>Stage III/IV, ( n ) (%)</td>
<td>7 (58.3)</td>
<td>6 (50.0)</td>
<td>9 (52.9)</td>
<td>12 (70.6)</td>
<td>5 (45.5)</td>
<td>7 (58.3)</td>
<td>6 (54.5)</td>
<td>7 (65.6)</td>
<td>0.929</td>
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<td>Extranodal</td>
<td>3 (25.0)</td>
<td>4 (33.3)</td>
<td>4 (23.5)</td>
<td>2 (11.8)</td>
<td>2 (18.2)</td>
<td>4 (33.3)</td>
<td>1 (9.1)</td>
<td>2 (18.2)</td>
<td>0.752</td>
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<td>development &gt; 1, ( n ) (%)</td>
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<td>IPI 1, -2, ( n ) (%)</td>
<td>6 (50.0)</td>
<td>7 (58.3)</td>
<td>9 (52.9)</td>
<td>8 (41.7)</td>
<td>6 (54.5)</td>
<td>6 (50.0)</td>
<td>6 (54.5)</td>
<td>6 (54.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>IPI 3-5, ( n ) (%)</td>
<td>6 (50.0)</td>
<td>5 (41.7)</td>
<td>8 (47.1)</td>
<td>9 (52.9)</td>
<td>5 (45.5)</td>
<td>6 (50.0)</td>
<td>5 (45.5)</td>
<td>5 (45.5)</td>
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</tbody>
</table>

One patient without data on BSA.

CHOP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHOP, combination immunochemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone; Peg, pegfilgrastim; BSA, body surface area per square meter; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; UNV, upper normal value; IPI, international prognostic index.

Figure 1. Trial profile. After randomization into the four different immunochemotherapy arms was stopped in the synchronously conducted RICOVER-60 trial [9] due to superiority of the arm with six cycles of CHOP-14 plus eight applications of rituximab, six patients who had already started the assigned treatment with 6x CHOP-14 without rituximab and pegfilgrastim day 2 (1*) and day 4 (2*) or to 8x CHOP-14 without rituximab and pegfilgrastim day 2 (1*) and day 4 (2*) were switched to receive six cycles with CHOP-14 with eight applications of rituximab. The last 12 patients recruited were all directly assigned to 6x CHOP-14 with eight applications of rituximab and randomly assigned to receive pegfilgrastim day 2 (\( n = 6^* \)) or day 4 (\( n = 6^* \)). CHOP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone.
between the two schedules of pegfilgrastim application (data not shown).

Adherence to protocol and feasibility of the chemotherapy regimen
The median total treatment duration was not different in the two arms: the median overall treatment duration after day 2 pegfilgrastim was 73 days for patients receiving six cycles of CHOP-14 (planned treatment duration 71 days) and 113 days for patients receiving eight cycles (planned treatment duration 109 days). Because dose reductions were only allowed if the treatment delay was >7 days, this strict adherence to the time schedule resulted in excellent median relative doses of the myelosuppressive drugs cyclophosphamide and doxorubicin of ≥98% with slightly more dose erosion in the day 2 arm (Figure 4). Similarly, the relative dose intensities for these drugs were 90% in patients assigned to day 2 and 93% in patients assigned to day 4 pegfilgrastim (P = 0.271), with no differences between the two pegfilgrastim schedules regarding response to therapy (rate of complete remissions 75% versus 77% in the day 2 and day 4 pegfilgrastim arms, respectively), event-free survival, progression-free survival and overall survival after a median time of observation of 3 years (data not shown). Similarly, the efficacy of the various chemotherapy arms in this trial was not different from the one observed in the RICOVER-60 trial [9], where filgrastim and lenograstim were used instead of pegfilgrastim.

Infections and deaths during leukocytopenia
There were more chemotherapy cycles with grade 3 and 4 infections after day 2 than day 4 pegfilgrastim (9.4% versus 6.0%; P = 0.118) and more patients in the day 2 arm experienced at least one grade 3 or 4 infection (38.3% versus 26.5%; P = 0.218). Prophylactic levofloxacin starting on day 7 of each chemotherapy cycle was recommended for all patients. Additional (interventional) antibiotics were used more often after day 2 than after day 4 pegfilgrastim (30.7% versus 21.9% of cycles; P=0.008) and interventional antibiotics were given to more patients in the day 2 arm than in the day 4 arm (70.8% versus 57.1%; P=0.16). There were five therapy-associated deaths during leukocytopenia after day 2 and none after day 4 pegfilgrastim (P=0.027). The five deaths in the 292 cycles with day 2 pegfilgrastim included four deaths due to infection (three pneumonias and one sepsis of an unknown cause) and one death due to an unknown cause. This patient was found dead at home and no autopsy was carried out. Since the patient’s death occurred on day 9, when the...
leukocyte nadir is expected, an overwhelming infection is the most likely cause.

**discussion**

To the best of our knowledge, this is the first trial demonstrating a benefit of delayed application of pegfilgrastim compared with the recommended early application. Administration of pegfilgrastim is recommended 24 h after chemotherapy, at a time point before the myelosuppressive effects of cytotoxic drugs reduce the neutrophil pool. Because neutrophil-mediated clearance is the major route of pegfilgrastim elimination, we presumed that deferring the administration until the neutrophils start to drop should result in a reduced clearance with consecutively higher pegfilgrastim serum levels during the nadir and thereafter that might be associated with a favorable effect on chemotherapy-induced leukocytopenia. Additional data favoring a later application of pegfilgrastim come from bioinformatics modeling of granulocytopoiesis [16–18]. In order to test this hypothesis, we started a randomized trial comparing the effects of pegfilgrastim given on day 4—when leukocytes usually start to drop—instead of day 2 of a 1-day chemotherapy regimen.

This randomized comparison with 103 elderly patients with untreated CD20+ aggressive lymphomas showed that day 4 application of pegfilgrastim has a positive effect on the absolute leukocyte nadir and is associated with significantly fewer chemotherapy cycles with grade 4 leukocytopenias, chemotherapy cycles where interventional antibiotics were given, and, most importantly, significantly fewer deaths during chemotherapy-induced leukocytopenia. There was no leukocytopenia-associated death after the 313 chemotherapy cycles with day 4 pegfilgrastim.

As the favorable effect of day 4 application on the course of leukocyte counts was observed in both female and male patients (Figure 3), the worse outcome of the day 2 pegfilgrastim patients in this study cannot be attributed to the overrepresentation of women in the day 2 pegfilgrastim arm. Median BSA was (insignificantly) lower in the group of patients assigned to day 2 pegfilgrastim. While the cytotoxic drugs were adjusted to BSA, the pegfilgrastim dose was fixed at 6 mg. Due to this fixed pegfilgrastim dose, day 2 pegfilgrastim patients with their lower BSA should have had higher pegfilgrastim concentrations and hence higher serum levels, but the opposite was the case. Whether the observed higher post-nadir day 4 serum levels are due to less clearance as a result of the fact that day 4 pegfilgrastim encounters less leukocytes or whether the higher post-nadir serum levels of day 4 pegfilgrastim just mirror the fall of pegfilgrastim serum levels expected over 2 days cannot be decided. Since post-nadir levels were higher after day 4 application, one can assume that this was also the case during myelosuppression, when differences in pegfilgrastim levels affect myeloprotection and neutrophil recovery, thus explaining the more favorable course of leukocytopenia after day 4 application.

The results of the RICOVER-60 trial [9] with 1222 patients had revealed a total of 23.7% grade 3 and 34.4% grade 4 leukocytopenias after the 2-week application of CHOP-14 with the use of filgrastim or lenograstim, respectively. Assuming a comparable efficacy of day 2 administration of pegfilgrastim, we expected similar figures with day 4 pegfilgrastim. Remarkably, pegfilgrastim application on day 2 resulted in higher grade 4 leukocytopenias (47.0%). With all the caveats of such nonrandomized comparisons between the RICOVER-60 trial and the simultaneously run DSHNHL 2003-2 study, this suggests that day 2 pegfilgrastim is associated with more grade 4 leukocytopenias than conventional G-CSF (filgrastim or lenograstim) application, while day 4 appears to be more effective than the conventional G-CSF.

While several nonrandomized comparisons of same-day and next-day pegfilgrastim had suggested that both schedules have similar antymyelosuppressive capacity [19], the only randomized comparison between the day 1 and day 2 schedule reported to date observed a longer duration of grade 4 neutropenia with the same-day schedule in patients with non-Hodgkin lymphomas receiving CHOP-21. This is in line with and extends the results of our study that demonstrated superiority of day 4 over day 2 administration in 2-week chemotherapy cycles (R-CHOP-14). While both studies were done in lymphoma patients, one can expect that similar effects would be obtained with other

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**Table 2.** Incidence of leukocytopenia (CTC grade 3 and 4)

<table>
<thead>
<tr>
<th></th>
<th>Pegfilgrastim on day 2</th>
<th>Pegfilgrastim on day 4</th>
<th><em>P</em> value</th>
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</thead>
<tbody>
<tr>
<td>CTC 3, 4 (% of cycles)</td>
<td>70.0</td>
<td>43.4</td>
<td>&lt;0.001a</td>
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<tr>
<td>(&lt;2 × 10³/mm³)</td>
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<tr>
<td>CTC 4 (% of cycles)</td>
<td>47.0</td>
<td>20.5</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>(&lt;1 × 10³/mm³)</td>
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</tr>
<tr>
<td>CTC 3, 4 (% of patients)</td>
<td>84.4</td>
<td>70.3</td>
<td>0.166</td>
</tr>
<tr>
<td>(&lt;2 × 10³/mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC 4 (% of patients)</td>
<td>65.6</td>
<td>43.2</td>
<td>0.063</td>
</tr>
<tr>
<td>(&lt;1 × 10³/mm³)</td>
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</tbody>
</table>

*Coefrane–Armitage test for trend: *P* < 0.001.

CTC, Common Toxicity Criteria.

**Figure 4.** Relative dose of cyclophosphamide. While the median dose with pegfilgrastim day 2 was 98% and thus nearly equivalent to the 99% with pegfilgrastim day 4, the cumulative dose plots show that there is more dose erosion with pegfilgrastim day 2.
Acknowledgements


Funding

Deutsche Krebshilfe; Amgen.

Disclosure

The authors declare no conflicts of interest.

References