Hematopoietic effects of recombinant human interleukin-3 and interleukin-6
Veldhuis, Gerrit Jan

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
1997

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Veldhuis, G. J. (1997). Hematopoietic effects of recombinant human interleukin-3 and interleukin-6
Groningen: s.n.
Recombinant human interleukin-3 to dose intensify carboplatin and cyclophosphamide chemotherapy in epithelial ovarian cancer: a phase I trial


Division of Medical Oncology, Department of Internal Medicine, Department of Gynaecology and Obstetrics¹, University Hospital Groningen, Groningen, The Netherlands; Department of Clinical Research Sandoz Ltd², Basel, Switzerland

Abstract

**Purpose.** To define the optimal recombinant human interleukin-3 (rhIL-3) dose required to intensify the dose of carboplatin and cyclophosphamide chemotherapy for primary advanced epithelial ovarian cancer.

**Patients and Methods.** Seventeen patients were treated on day one with carboplatin (dose adjusted for creatinine clearance, range 257-385 mg/m², median 300 mg/m²) and cyclophosphamide (750 mg/m²). RhIL-3 5 µg/kg/day (n=10) or 10 µg/kg/day (n=7) was administered subcutaneously on days 2 through 11. Carboplatin dose was to be escalated if no postponement of cycle 1-3 had occurred.

**Results.** A three week chemotherapy interval could be achieved in 62% of the cycles and within a four week interval in 81%, with no difference between the two rhIL-3 doses. A neutrophil nadir less than 0.5×10⁹/l occurred in 35% of the cycles at 5 µg/kg/day rhIL-3 and in 52% at 10 µg/kg/day (N.S.). The mean platelet nadir in cycle 1 was 173±78×10⁹/l at 5 µg/kg/day rhIL-3 and 340±152×10⁹/l at 10 µg/kg/day rhIL-3 (p<0.05), with a faster recovery of platelets at 10 µg/kg/day (p<0.05). Progressive myelotoxicity occurred for leukocytes and platelets at both rhIL-3 doses, and required chemotherapy postponement in later cycles. The planned six cycles were completed by 41% of the patients. Fever (≥ 38.5°C) occurred in 38% of the cycles at 5 µg/kg/day rhIL-3 and in 97% at 10 µg/kg/day (p<0.0005). Headache and myalgias occurred in 30% and 44% of the cycles on 5 and 10 µg/kg/day rhIL-3, respectively. After two cycles, diffuse erythema, facial edema and urticaria was observed in two patients at 5 µg/kg/day and in five patients at 10 µg/kg/day rhIL-3. These side effects resolved after discontinuation of rhIL-3 and administration of corticosteroids and antihistamines.

**Conclusion.** A dose of 5 µg/kg/day rhIL-3 proved to be optimal to intensify the carboplatin and cyclophosphamide regimen. It permitted the administration of carboplatin and cyclophosphamide combination therapy every three weeks in 62% of the cycles.
Introduction

Platinum-derived and alkylating agents are important drugs in primary advanced ovarian carcinoma [1]. Although cisplatin has been the mainstay of treatment in advanced ovarian carcinoma, its use is limited by nephro-, neuro- and ototoxicity [1-4]. Carboplatin, on the other hand, has shown equal activity, as compared to cisplatin, while being better tolerated with less nephro- and neurotoxicity, at the cost of dose-limiting myelosuppression (5-7). Several hemopoietic colony-stimulating factors are able to ameliorate myelosuppression by accelerating bone marrow restoration [8-11]. A reduction in chemotherapy related neutropenia has been demonstrated for granulocyte (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [12, 13]. Some studies have also suggested an effect for GM-CSF on platelets [14-17]. Compared to these cytokines, recombinant human interleukin-3 (rhIL-3) in vitro showed a stimulation of uncommitted progenitors [18-21]. Multilineage haemopoietic effects were observed in patients with normal bone marrow function and in patients with advanced malignancies and bone marrow failure [22-25]. Studies with rhIL-3 administered to patients receiving chemotherapy also showed some rhIL-3 induced platelet stimulation [26, 27]. In ovarian carcinoma patients who received rhIL-3 on alternate cycles, less chemotherapy delay occurred after a cycle in which rhIL-3 was administered [27]. Little, however, is known about the effects of rhIL-3 administered for multiple consecutive chemotherapy cycles.

In the present study rhIL-3 was administered at two potential optimal dose-steps (5 μg/kg/day and 10 μg/kg/day) for six consecutive chemotherapy cycles in previously untreated patients with advanced ovarian carcinoma. Dose intensification was attempted by reducing the chemotherapy interval from standard four to three weeks. Carboplatin dose was escalated in patients who showed no delay in the administration of chemotherapy in the initial three cycles.
Methods

Patients. Seventeen consecutive patients, between 18 and 70 years of age, with newly diagnosed stage Ic-IV ovarian cancer according to the International Federation of Gynecologists and Obstetricians (FIGO) and who were eligible for treatment with chemotherapy were entered in the study between June 1992 and August 1993. Patients underwent optimal tumor reductive surgery before the start of the chemotherapy, whenever possible. A leukocyte count of \( \geq 3 \times 10^9/\text{l} \) and a platelet count of \( \geq 100 \times 10^9/\text{l} \) was required at entry. Patients with severe heart, lung, liver (serum bilirubin \( \geq 40 \text{ mmol/l} \)) and renal impairment (creatinine clearance \(< 60 \text{ ml/min} \)) were excluded from the study, as were patients with a WHO performance score grade 3-4. Those previously treated with chemotherapy, or on treatment with steroids, morphine, cimetidine or other H\(_2\)-histamine blockers were not eligible for the study.

Study design. Combination chemotherapy comprised six cycles of cyclophosphamide (750 mg/m\(^2\)) and carboplatin (dose adjusted to creatinine clearance: 60-80 ml/min: 257 mg/m\(^2\), 80-120 ml/min: 300 mg/m\(^2\), 120-140 ml/min: 340 mg/m\(^2\) and >140 ml/min: 385 mg/m\(^2\)) both administered day 1 on an outpatient basis. The dosing regimen of carboplatin, based on carboplatin clearance, was derived from Calvert et al.\[28\] and modified according to Lindegaard et al.\[29\] with stratification in four cohorts. Cyclophosphamide (ASTA Pharma A.G., Frankfurt, Germany) dissolved in 250 ml saline 0.9%, was administered intravenously (iv) over 15 min, carboplatin (Bristol-Myers Squibb, Regensburg, Germany), dissolved in 250 ml dextrose 5%, was administered iv over 30 min.

E. coli derived nonglycosylated rhIL-3 (2-10\( \times 10^6 \) U/mg) was provided by Sandoz (Basel, Switzerland) in vials of 300 mg/ml. RhIL-3 was reconstituted for subcutaneous (sc) administration with 1 ml of sterile water. After instructions by the oncology nurse, rhIL-3 was self-administered sc in the upper leg by the patient on an outpatient basis. The patients were randomized to receive 5 or 10 \( \mu \)g/kg/day rhIL-3, for 10 days, starting 24 hours after chemotherapy administration. Chemotherapy was scheduled every three weeks. The next chemotherapy cycle was postponed up to a maximum of four weeks if insufficient recovery was observed (leukocytes \(< 3 \times 10^9/\text{l} \) and/or platelets \(< 100 \times 10^9/\text{l} \)), but the chemotherapy dose was not reduced. Platelet
transfusion was given if platelets were below $20 \times 10^9/l$ and/or if a bleeding tendency was observed. The dose of carboplatin was escalated by 33% if chemotherapy was not delayed in the three initial cycles and when platelet nadir had not been below $40 \times 10^9/l$. This escalated dose was administered in the fourth cycle, and continued in the following cycles.

All side effects were scored according to WHO criteria. Acetaminophen (maximum 3 g/day) was administered for headache, fever $\geq 38.5^\circ C$ (measured axillary), or myalgias. A patient was taken off study when tumor progression was observed or when non-hematological WHO grade III-IV toxicity occurred.

Physical examination, blood and differential counts were performed on day 1, 8, 15 and 22 of each cycle. Liver and renal function tests and serum levels of Na, K, Ca, total protein and albumin were determined on the same days. Evaluation of tumor parameters was performed before treatment and after six cycles according to WHO criteria.

The study was approved by the Medical Ethical Committee of the University Hospital Groningen. Written informed consent was obtained from all patients.

**Statistical analysis.** The two tailed Student’s t-test was used to compare mean values of hematological parameters, area under curve (AUC) and chemotherapy interval. Spearman rank analysis was used to calculate correlation coefficients between the number of chemotherapy cycles and platelet nadir or chemotherapy interval. The chi-square test for small numbers was used to test differences between both dose steps with regard to: the reason for chemotherapy postponement, frequencies of side effects, neutrophil nadir and tumor response. P-values less than 0.05 were considered significant. Unless otherwise stated, the two tailed Student’s t-test was applied.
Results

**Patient characteristics.** The median age of the patients entered in this study was 54 years (range 28-68 years). Ten patients received 5 µg/kg/day rhIL-3 and seven patients received 10 µg/kg/day rhIL-3. Seven patients were initially entered at each dose step. In view of the toxicity pattern additional patients were entered at the lowest dose. The dose of carboplatin was escalated in four patients. It was, however, not performed in additional eligible patients due to the observed side effects in the escalated cycles. Seven patients actually completed six chemotherapy cycles with rhIL-3 support while ten patients prematurely discontinued the study. Six patients discontinued the study due to side effects of rhIL-3 administration, while two patients stopped due to progressive disease. In the last phase of the study patients were hospitalized for observation after cycle two because of the observed urticaria combined with edema of the lips, eyelids and extremities. Two patients wanted to continue to receive their treatment on an outpatient basis, therefore necessitating the cessation of rhIL-3 treatment. Further details concerning both groups are shown in Table 1.

<table>
<thead>
<tr>
<th>rhIL-3 dose (µg/kg/day)</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>57 (40-68)</td>
<td>52 (28-62)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min, mean±SD)</td>
<td>82±33</td>
<td>94±22</td>
</tr>
<tr>
<td>Carboplatin dose (mg/m², mean±SD)</td>
<td>296±12</td>
<td>293±27</td>
</tr>
<tr>
<td>Disease classification (FIGO):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ic</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Hematological recovery. Seventy-four cycles with rhIL-3, 43 on 5 μg and 31 on 10 μg/kg/day rhIL-3, were evaluated for hematological effects. Table 2 illustrates the chemotherapy interval. Taken together: in 46 out of 74 cycles (62%) chemotherapy could be given after a three week interval, and in 60 out of 74 cycles (81%) it could be given after a four week interval. The effect of 5 or 10 μg/kg/day rhIL-3 was comparable with regard to chemotherapy interval.

Table 2. Length of chemotherapy interval at 5 and 10 μg/kg/day rhIL-3 (including carboplatin escalated cycles).

<table>
<thead>
<tr>
<th>rhIL-3 dose (μg/kg/day)</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy interval (weeks)</td>
<td>Number of cycles (%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25 (58)</td>
<td>21 (68)</td>
</tr>
<tr>
<td>4</td>
<td>10 (23)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>5</td>
<td>4 (9)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>6</td>
<td>3 (7)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>7</td>
<td>1 (2)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Table 3 lists the reasons for chemotherapy postponement. In 28 out of 74 cycles the interval was longer than three weeks. This was due to insufficient platelet recovery in 16 cycles and insufficient leukocyte recovery in 10 cycles, while in two cycles both platelets and leukocytes had not fully recovered. In four patients, in whom chemotherapy could be given on time in the initial three cycles, carboplatin dose was escalated in the fourth cycle. All of these patients (one on 5 and three on 10 μg/kg/day rhIL-3) experienced worsening of the constitutional symptoms during
rhIL-3 treatment, namely, fever, headache and myalgias. Furthermore, erythematous and urticarial skin reactions were observed in the escalated cycles, leading to premature discontinuation of the rhIL-3 in one patient (5 μg/kg/day rhIL-3) due to generalization of the urticaria. Two of the patients at 10 μg/kg/day rhIL-3 showed no chemotherapy delay, whereas the third had a delay of one week in the escalated cycle. This was comparable to the hematological recovery observed in the non-escalated cycles. Although there were no major differences in hematological recovery between escalated and non-escalated cycles, the results of the escalated cycles were not used in the calculations of mean blood counts shown in figures 1 and 3 to 7.

There is a gradual decrease in mean platelet nadir from cycle 1 to cycle 6 due to progressive myelotoxicity (Figure 1), also expressed by the gradual increase in chemotherapy cycle length (Figure 2). Based upon both this gradual decline in cell numbers and the small number of patients left in cycle six, it was determined that comparison of cycle one and cycle five would be the most representative for evaluating dose effects in this study.

**Table 3.** Reasons for chemotherapy postponement (including escalated cycles).

<table>
<thead>
<tr>
<th>rhIL-3 dose (μg/kg/day)</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Reason for postponement</th>
<th>Platelets &lt;100 x 10^9/l</th>
<th>Leukocytes &lt;3 x 10^9/l</th>
<th>Platelets &lt;100 x 10^9/l &amp; Leukocytes &lt;3 x 10^9/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 (67)</td>
<td>6 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>4 (40)</td>
<td>4 (40)</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>
Leukocytes reached a nadir in the first cycle of (mean±SD) 3.16±1.65 $\times 10^9$/l and 3.49±1.32 $\times 10^9$/l for 5 and 10 μg/kg/day rhIL-3, respectively (NS). The neutrophil nadir count, as shown in Figure 3, was 0.83±0.55 $\times 10^9$/l and 1.26±1.00 $\times 10^9$/l for 5 and 10 μg/kg/day rhIL-3, respectively (NS). The leukocyte nadir was lower in the fifth cycle: 1.83±0.29 $\times 10^9$/l (nadir cycle 1 vs cycle 5, p<0.05) and 1.45±0.25 $\times 10^9$/l (nadir cycle 1 vs nadir cycle 5, NS) for 5 and 10 μg/kg/day rhIL-3, respectively. The leukocyte nadir in the fifth cycle did again not differ for 5 and 10 μg/kg/day rhIL-3. The AUC for leukocytes showed a significant decrease in the fifth cycle compared to the first cycle (Table 4). The neutrophil nadir in the fifth cycle was 0.64±0.38 $\times 10^9$/l and 0.22±0.09 $\times 10^9$/l for 5 and 10 μg/kg/day rhIL-3, respectively (NS between rhIL-3 dose steps). Nadir of leukocytes and neutrophils was observed about two weeks after rhIL-3 to dose intensify carboplatin and cyclophosphamide chemotherapy.
Figure 3. Mean neutrophil counts in patients at 5 (●) and 10 μg/kg/day rhIL-3 (■) in cycle one (●) and cycle five (■).

Figure 4. Mean basophil counts in patients at 5 (●) and 10 μg/kg/day rhIL-3 (■) in cycle one (●) and cycle five (■).

Figure 5. Mean eosinophil counts in patients at 5 (●) and 10 μg/kg/day rhIL-3 (■) in cycle one (●) and cycle five (■).

Figure 6. Mean platelet counts in patients at 5 (●) and 10 μg/kg/day rhIL-3 (■) in cycle one (●) and cycle five (■).
chemotherapy in the first cycle and fifth cycle. Neutrophil nadir below $0.5 \times 10^9/l$ was observed in 15/43 (35%) and 16/31 (52%) cycles (NS) for 5 and 10 μg/kg/day rhIL-3, respectively. No clinically or bacterially proven infection occurred, nor was neutropenic fever observed at both dose steps.

Table 4. Area under curve (blood count x days) for peripheral blood cells in cycle one and cycle five (% compared to cycle 1).

<table>
<thead>
<tr>
<th>rhIL-3 dose (μg/kg/day)</th>
<th>Cycle</th>
<th>Leukocytes</th>
<th>Neutrophils</th>
<th>Basophils</th>
<th>Eosinophils</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>1</td>
<td>99</td>
<td>49</td>
<td>0.46</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>55</td>
<td>36</td>
<td>0.15</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(56)</td>
<td>(73)</td>
<td>(33)</td>
<td>(39)</td>
<td>(59)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1</td>
<td>118</td>
<td>78</td>
<td>1.25</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>44</td>
<td>20</td>
<td>0.26</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(37)</td>
<td>(26)</td>
<td>(21)</td>
<td>(11)</td>
<td>(38)</td>
</tr>
</tbody>
</table>

An initial decrease in basophils was observed in the first cycle for both groups; with its nadir about seven days after chemotherapy. Basophils increased subsequently while neutrophils and platelets decreased, but the number of basophils never exceeded $0.2 \times 10^9/l$ (Figure 4). An impressive effect was observed on eosinophil counts (Figure 5). The number of eosinophils increased from $0.12 \pm 0.12 \times 10^9/l$ before chemotherapy to $0.61 \pm 0.41 \times 10^9/l$ after one week ($p<0.02$ versus day 1) and from $0.20 \pm 0.10 \times 10^9/l$ to $0.74 \pm 0.49 \times 10^9/l$ (NS versus day 1) for 5 and 10 μg/kg/day rhIL-3, respectively ($408$ and $254\%$ increase for 5 and 10 μg/kg/day rhIL-3, respectively). They returned to baseline values at the end of the first cycle. This increase during rhIL-3 treatment was still present but smaller in the fifth cycle. As was the case for
leukocytes, there was a decrease in neutrophils, basophils and eosinophils as expressed by mean AUC in the fifth cycle as compared to the first cycle (Table 4). There was, however, no statistically significant difference between both rhIL-3 dose steps.

The platelet nadir in the first cycle, as shown in Figure 6, occurred one week after chemotherapy for patients on 10 μg/kg/day rhIL-3, and was $266\pm111 \times 10^9/l$, and after two weeks for patients on 5 μg/kg/day rhIL-3 with a mean of $173\pm78 \times 10^9/l$ (nadir difference NS between dose-steps). Platelet recovery was seen earlier for those on 10 μg/kg/day rhIL-3 than for patients on 5 μg/kg/day rhIL-3 in the first cycle (day 15, p<0.05 between dose steps). In the fifth cycle the platelet nadir occurred two weeks after chemotherapy at the 5 μg/kg/day rhIL-3 dose level and around day 22 for those on 10 μg. When cycle one and five were compared there appeared to be progressive myelotoxicity for platelets, as expressed by AUC (Table 4). Platelet transfusion was given only once. This was administered to a patient who received an escalated dose of carboplatin in the fourth cycle on 10 μg/kg/day rhIL-3 for platelets <20 $\times 10^9/l$ without showing a bleeding tendency.

**Tumor response.** Four and five patients at 5 and 10 μg/kg/day rhIL-3, respectively, showed a complete response to treatment. Four patients showed a partial response and two showed progressive disease at the lowest rhIL-3 dose. There was one patient with stable disease and one with progressive disease at 10 μg/kg/day rhIL-3 (NS between 5 and 10 μg/kg/day rhIL-3 dose, Chi-square).

**Side-effects of treatment.** Seventy-nine cycles, 46 at 5 μg and 33 at 10 μg/kg/day rhIL-3, were evaluable for toxicity. A summary of the side-effects is given in Table 5. Fever, headache, rash and myalgias were reported more often by those patients receiving a dose of 10 μg/kg/day rhIL-3. These symptoms responded well to acetaminophen administration. Facial flushing was observed exclusively after the first rhIL-3 administration. Urticaria occurred in eight cycles for five patients, urticaria combined with edema of the lips, the eyelids, and the extremities was observed in seven cycles. Conjunctivitis was reported in five cycles. Two patients experienced a
subjective feeling of dyspnea, and one patient had atypical chest pain shortly after the first rhIL-3 administration. Physical examination and electrocardiography revealed no abnormalities. These symptoms all resolved after discontinuation of the rhIL-3 injections. The rhIL-3 administration was discontinued prematurely in nine cycles because of side-effects. It concerned three cycles in two patients at 5 mg and six cycles in five patients at 10 mg/kg/day rhIL-3. Erythema, urticaria and facial edema were, either alone or in combination, the most frequent reasons for discontinuing the rhIL-3. These reactions subsided quickly after administration of corticosteroids and antihistamines. No recurrences were observed in patients in whom rhIL-3 was discontinued while chemotherapy was continued. Two patients who had experienced urticaria during treatment were rechallenged with rhIL-3 and chemotherapy without

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>rhIL-3 dose</th>
<th>Number of cycles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Fever WHO grade I-II</td>
<td>18 (39)</td>
<td>32 (97) *</td>
</tr>
<tr>
<td>Headache and myalgias</td>
<td>14 (30)</td>
<td>14 (42)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>4 (9)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Facial erythema/flushing</td>
<td>3 (7)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Generalized erythema</td>
<td>6 (13)</td>
<td>15 (45) **</td>
</tr>
<tr>
<td>Urticaria</td>
<td>3 (7)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Facial edema</td>
<td>3 (7)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0 (0)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

* p < 0.0005 (5 µg/kg/day rhIL-3 vs 10 µg)
** p < 0.005 (5 µg/kg/day rhIL-3 vs 10 µg), Chi-square
Chapter 3

recurrences. The mechanism of these side effects remains obscure; histamine and histamine metabolites determined in urine samples and complement factors in blood samples of these patients were within the normal range. The eosinophil and basophil counts from these patients did not differ from patients without these phenomena. These, more serious, reactions were all observed after the initial two courses. In the first two cycles, apart from fever and headache, only flushing, conjunctivitis and some edema of the hands was observed. The patients who received an escalated dose of carboplatin all experienced erythematous and urticarial skin reactions (NS compared to non-escalated cycles).

Discussion

In the present study rhIL-3 was administered for maximally six consecutive cycles. The chemotherapy interval was shortened to three weeks in 62% of the assessable cycles. In 81% of the cycles chemotherapy could still be given within four weeks. Compared with previous studies, an indicative dose intensification could be reached by addition of rhIL-3. In a study with the same chemotherapy regimen, Biesma et al. found that chemotherapy postponement was necessary due to prolonged myelotoxicity in 48% of four-week cycles without growth factor support [27]. Longer chemotherapy intervals were observed in another study with the same regimen in patients treated without growth factor support [17]. In our study, there was a faster platelet recovery in the first cycle at 10 μg/kg/day rhIL-3 than at 5 μg/kg/day. This effect disappeared in the fifth cycle. RhIL-3 effects on other peripheral blood cells were not dose related. D’Hondt reported a rhIL-3 dose dependent increase in platelet and neutrophil recovery [30]. Biesma et al. could not demonstrate a rhIL-3 dose related effect on leukocytes and in platelets [27].

In our study, rhIL-3 administration in consecutive chemotherapy cycles was studied. As a result of progressive myelotoxicity, e.g. for platelets (Figure 1), a gradual increase was observed in chemotherapy interval (Figure 2). However, compared to other studies that have used the same chemotherapy regimen [17, 27], fewer platelet transfusions were required in this setting. Dose escalation of carboplatin did not
rhIL-3 to dose intensify carboplatin and cyclophosphamide chemotherapy

prove to be successful due to an increased frequency of side effects in these cycles, i.e. all patients experienced erythematous and urticarial skin reactions. However, no statistical significance could be reached concerning the frequencies of side effects in carboplatin escalated cycles compared to non-escalated cycles. Probably this was purely coincidental, because dose escalation of carboplatin was performed after the third cycle and most rhIL-3 related side effects occurred after several cycles. No major differences were observed in hematological recovery in carboplatin escalated cycles as compared to non-escalated cycles.

The small sample size does not allow firm conclusions, but a complete pathological response rate of nine out of 17 patients is in accordance with results reported by others [31,32].

The toxicity profile of rhIL-3 observed in this study was almost identical to that reported by others [26,27,30,33-35]. However, an increase in the severity of toxicity was observed during rhIL-3 treatment over several cycles. Side effects were tolerable, without necessity to stop rhIL-3 treatment in the first two cycles. Erythema, urticaria and edema, were reasons to terminate treatment with rhIL-3 from the third cycle onwards. This pattern of increasing toxicity was not observed in a study performed with 26 patients treated with the same chemotherapeutic regimen and rhIL-3 administered in three cycles, alternated with cycles without growth factor support [27]. Previous work showed that IL-3 may be involved at various levels of allergic inflammation [36-39]. In preclinical and clinical studies it was shown that basophils incubated in vitro with rhIL-3 released histamine [40-43]. Furthermore, rhIL-3 induced enhanced formation of basophils and eosinophils [42] and a morphological change of eosinophils characteristic for activation [44]. No increased histamine release was found in urine samples in other studies [22-25, 27]. In our study there was a rapid resolution of the side effects after administration of corticosteroids and antihistamines. The absolute number of eosinophils increased during treatment with rhIL-3. Basophils, although less pronounced than eosinophils, were detectable in peripheral blood even after several chemotherapy cycles. Histamine and histamine metabolite urine levels as well as serum complement factors remained within the normal range in patients experiencing allergic phenomena. However, the more serious side effects were all observed after more than two cycles, while the increase in
eosinophils was gradually blunted. Basophils were present in all cycles during rhIL-3 treatment in higher concentrations than would be expected during treatment with chemotherapeutic agents alone. Redistribution or consumption can not be excluded with respect to the initial decrease in basophils in the first cycle. Platinum compounds are known to cause allergic reactions, especially shortly after administration [45]. In the present study, a potential involvement of the chemotherapeutic drugs in allergic reactions can not be excluded. Rechallenging with carboplatin and cyclophosphamide in two patients after premature discontinuation of rhIL-3 was uneventful.

In this phase I study, an indicative dose intensification of carboplatin/cyclophosphamide regimen could be achieved by addition of rhIL-3, without a difference in hematological efficacy between 5 and 10 \( \mu \text{g/kg/day} \) rhIL-3. A lower rate of side effects was reported for patients receiving 5 \( \mu \text{g/kg/day} \) rhIL-3, but the nature of the side effects still remains unclear. Additional studies are in progress to elucidate the mechanism of these side effects, in order to develop prophylactic measures for the future. A phase III study is currently being performed to evaluate the effects of rhIL-3 on dose intensity of chemotherapy.

References


