Effects of Interleukin-3 After Chemotherapy for Advanced Ovarian Cancer


To define the maximum tolerated dose and to study whether recombinant human interleukin-3 (rhIL-3) reduced chemotherapy-induced neutropenia and thrombocytopenia, 20 chemotherapy-naive patients with advanced ovarian cancer eligible for treatment with 6 cycles of carboplatin-cyclophosphamide every 4 weeks (day 1) were entered into a phase I/II open, single-center trial. Cohorts of five patients received during 7 cycles every 4 weeks (day 1 every 4 weeks) single-center trial. Cohorts of five patients received during 7 cycles every 4 weeks (day 1, 5, 10, or 15 μg/kg/d rhIL-3 (days 5 through 11) in cycles 1, 3, and 5 by continuous intravenous (IV) infusion or once daily subcutaneous (SC) administration. In control cycles 2, 4, and 6, no rhIL-3 was administered. rhIL-3 significantly increased the recovery of leukocyte, neutrophil, and lymphocyte counts at this dose steps. Effects on reticulo-platelet counts, especially at day 15, were limited. No difference in efficacy between SC and IV rhIL-3 treatment was found. Chemotherapy postpone-ment for insufficient bone marrow recovery was necessary in 22 of 45 control cycles versus 2 of 49 rhIL-3 cycles (P < .001). Platelet transfusions were required in 7 of 45 control cycles versus 3 of 50 rhIL-3 cycles (P < .5). rhIL-3 up to 10 μg/kg/d could be administered without severe side effects. At 15 μg/kg/d, rhIL-3 headache was dose-limiting. Other side effects were fever, flu-like symptoms, nausea, skin rash, flushing, facial erythema, and urticaria. Liver toxicity oc-urred in rhIL-3 and control cycles. rhIL-3 slightly increased tumor necrosis factor α, C-reactive protein, and serum amy-loid A plasma levels, whereas no effect on IL-6 plasma levels was observed. rhIL-3 administered SC appears to be an interesting hematopoietic growth factor for reduction of chemotherapy-induced myelotoxicity.

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MATERIALS AND METHODS

Patients. Twenty consecutive patients, between 18 and 70 years of age, with stage III-IV ovarian cancer according to the Interna-tional Federation of Gynecologists and Obstetricians (FIGO) and eligible for treatment with chemotherapy were entered into the study. At entry, a leucocyte count ≥ 3.0 × 10^9/L and a platelet count ≥ 100 × 10^9/L were required. Patients with severe heart, lung, liver (serum total bilirubin > 40 μmol/L), or kidney impair-ment (creatinine clearance ≤ 50 mL/min) were excluded from the study, as were patients with a World Health Organization (WHO) performance score grade 3-4. Those previously treated with chemother-a or on treatment with steroids, morphine, or cimstidine and analogues were not eligible for the study. Whenever possible, patients underwent tumor-reductive surgery before the start of chemotherapy.

Study design. Combination chemotherapy comprised six courses of carboplatin (300 mg/m^2) and cyclophosphamide (750 mg/m^2), both administered intravenously (IV) on day 1 every 4 weeks on an outpatient basis. Carboplatin (Bristol-Myers, Troisdorf, Germany), dissolved in 250 mL 5% dextrose, was infused over 30 minutes.

From the Division of Medical Oncology, Department of Internal Medicine, and the Departments of Rheumatology, Oncologic Gynecology, and Hematology, University Hospital Groningen, Groningen, The Netherlands; and the Department of Clinical Research, Sandoz Ltd, Basle, Switzerland.

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Address reprint requests to Elizabeth G.E. de Vries, MD, Division of Medical Oncology, Department of Internal Medicine, University Hos-pital, Oosterwegel 59, 9713 EZ Groningen, The Netherlands.

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Cyclophosphamide (ASTA Pharma A.G., Frankfurt, Germany), dissolved in 250 mL 0.9% saline, was infused over 15 minutes. Chemotherapy dose reduction was not applied. Treatment was postponed, up to a maximum of 4 weeks, when insufficient BM recovery (leukocytes <3 x 10^9/L or platelets <100 x 10^9/L) occurred. Platelet transfusions were administered at the platelet count less than 20 x 10^9/L or when signs of bleeding tendency occurred.

E. coli-derived rhIL-3 (2 to 10 x 10^6 U/mg protein) was provided by Sandoz (Basle, Switzerland) in vials of 150 μg (for IV infusion) and 300 μg (for subcutaneous [SC] infusion). For the daily IV infusion, polypropylene syringes were used for each of the two 12-hour infusions, containing half of the daily rhIL-3 dosage, 96 mg (2 mg/mL) human serum albumin, and 0.9% saline, with a total volume of 48 mL. rhIL-3 in the syringes remained stable for 24 hours. For SC administration, rhIL-3 was reconstituted with 1 mL sterile water. After instructions by the oncology nurse, rhIL-3 was injected SC in the upper leg, on an outpatient basis. If the volume exceeded 4 mL, the dosage was divided over both upper legs.

In this phase I/II study, the patients were divided into five groups of five patients each. After the first, third, and fifth chemotherapy course, each group received 1, 5, 10, or 15 μg/kg/d rhIL-3 for 7 days (days 5 through 11), starting 4 days after chemotherapy (day 1). To study a possible difference in tolerability, the patients were randomized for either continuous IV or once daily SC rhIL-3 administration in cycle 1. In cycle 3, the route of administration was reversed. During cycle 5, all patients received rhIL-3 SC. For evaluation of hematologic effects, no rhIL-3 was administered in cycles 2, 4, and 6 (control cycles). The maximum tolerated dose (MTD) was defined as the dose level preceding that at which at least two patients experienced WHO grade III or IV toxicity or life-debilitating toxicity leading to discontinuation of rhIL-3 administration. Acetaminophen (maximum 3 g/d) was administered when headache, fever greater than 38.0°C (measured axillary), or flu-like symptoms occurred.

If tumor progression occurred, the patient was taken off study. The study was approved by the Medical Ethical Committee of the University Hospital of Groningen. Informed consent was obtained from all patients.

Blood counts, including differential counts, were performed on days 1, 8, 13, 15, and 22 during each cycle. Liver and renal functions and serum levels of sodium, potassium, calcium, total protein, and albumin were determined on days 1, 8, 15, and 22. Blood pressure, temperature, body weight, and heart rate were measured daily during rhIL-3 administration and every 2 weeks during the control cycles. Creatinine clearance was calculated from the creatinine levels in 24-hour urine and in serum. Tumor necrosis factor-α (TNF-α), IL-6, C-reactive protein (CRP), and serum amyloid A (SAA) plasma levels were determined during IV and SC rhIL-3 administration in all patients. The plasma samples were taken on day 1 before chemotherapy, on day 5 (before rhIL-3 administration), and on days 6, 7, 11, and 14 or 15. TNF-α (detection limit, 5 ng/L) was measured with a radioimmunoassay (Medgenix, Brussels, Belgium), IL-6 (normal value, <10 U/mL) with the B9 bioassay, and CRP (normal value, <2 mg/L) and SAA (normal value, <3 mg/L) with enzyme-linked immunosorbent assays. Urinary methylhistamine (normal value, 0 to 150 μmol/mol creatinine) and methylimidazoleacetic acid (normal value, 0.5 to 2.5 mmol/mol creatinine) levels in 24-hour urine were measured on days 1, 5, and 11, as described before.

Statistical analysis. The two-tailed Student’s t-test, the χ² test for small numbers, the Kruskal-Wallis analysis of variance, and the Wilcoxon rank sum test were used for statistical analysis. P values <.05 were considered significant. Unless otherwise stated, the two-tailed Student’s t-test was used for statistical analysis.

RESULTS

Patient characteristics. The median age of the patients entered in the study was 59.5 years (range, 21 to 69). Sixteen patients presented with stage III ovarian cancer, while four patients were diagnosed with stage IV. Creatinine clearance (mean ± SD) at entry was 100 ± 14 mL/min, 89 ± 28 mL/min, 117 ± 24 mL/min, and 109 ± 10 mL/min in the 1, 5, 10, and 15 μg/kg/d IL-3 dose groups, respectively (not significant [NS] for all dose steps).

Hematologic recovery. Fifty cycles with rhIL-3 (1 μg, 12 cycles; 5 μg, 13 cycles; 10 μg, 15 cycles; 15 μg, 10 cycles) and 45 control cycles were evaluable for hematologic effects. Two cycles with rhIL-3 at 15 μg were not evaluable because of premature discontinuation of rhIL-3 due to toxicity. Progressive myelotoxicity in consecutive chemotherapy courses could not be demonstrated in this study, as the area under the curve for the neutrophils and platelets, expressed as percentage change from day 1, did not differ between control cycles 2 and 6 (P <.02, Wilcoxon rank sum test). SC and IV administration of rhIL-3 resulted in similar effects on neutrophil counts (day 22: SC, 3.01 ± 1.70 x 10^9/L; IV, 3.24 ± 2.21 x 10^9/L; n = 16) and platelet counts (day 22: SC, 318 ± 168 x 10^9/L; IV, 333 ± 134 x 10^9/L; n = 16). At the 10 and 15 μg/kg/d dose steps, the mean leukocyte count was raised at all time points compared with the control cycles (Fig 1). At 5 μg, effects on the leukocyte count on day 15 and on the recovery of the leukocyte count (day 22) were also observed.

rhIL-3 demonstrated an effect on the neutrophil nadir (Fig 2) at 10 μg/kg/d (day 15: control, 0.58 ± 0.51 x 10^9/L; 10 μg, 1.15 ± 1.29 x 10^9/L; P <.02). However, this effect at 10 μg could not be demonstrated when neutrophil counts on day 15, expressed as percentage changes from day 1 of each cycle, were compared with the control cycles at the same dose step (Wilcoxon rank sum test). The recovery of the neutrophil counts was hastened at 5, 10, and 15 μg. The
neutrophil counts at these doses were higher on day 22 compared with the control cycles. This was also the case for percentage changes from day 1 compared with the control cycles at each dose step (Wilcoxon rank sum test). In addition, the recovery was faster at the 5, 10, and 15 µg dosages compared with the 1 µg dose (Kruskal-Wallis analysis of variance, \( P < .05 \)). The faster recovery was caused mainly by increases in segmented neutrophils. The neutrophil count on day 29, the day the next chemotherapy course was scheduled, was higher at all rhIL-3 doses than in the control cycles.

Monocyte counts were raised at the 5 to 15 µg doses (Fig 4). The most pronounced effect was observed at 10 µg rhIL-3. For the eosinophils, rhIL-3 demonstrated a dose-response effect, with the highest counts on day 13, especially at 15 µg (Fig 5). An effect on the basophil counts was apparent mainly at the 5, 10, and 15 µg dose steps. However, this was probably of little clinical interest, as the basophil counts never exceeded \( 0.2 \times 10^9/L \). Lymphocyte counts were affected at 10 and 15 µg (Fig 6).

The mean platelet count (Fig 7) on day 15, the day of nadir, was raised at the 10 µg dose compared with the control cycles (control, \( 82.6 \pm 60.5 \times 10^9/L \); 10 µg, \( 151.7 \pm 99.7 \times 10^9/L \); \( P < .01 \)). However, as for the neutrophil counts, this effect at 10 µg could not be demonstrated when platelet counts on day 15, expressed as percentage changes from day 1 of each cycle, were compared with the control cycles at the same dose step (Wilcoxon rank sum test). At 1 and 5 µg, platelet transfusions were necessary in 3 of 25 cycles with rhIL-3 (1 µg, 1 of 12 cycles; 5 µg, 2 of 13 cycles), whereas no platelet transfusions were necessary at 10 and 15 µg. Platelet transfusions were needed in 7 of 45 control cycles (\( P < .5 \)). In addition, the recovery of the platelet count (day 22) was faster at all rhIL-3 doses. This was also the case for percentage changes from day 1 compared with the control cycles at each dose step (Wilcoxon rank sum test). In Table 1, the platelet counts on days 1 and 22 in each cycle of all patients at the 10 µg/kg/d dose step are shown. No difference in recovery between the different dose steps could be demonstrated (Kruskal-Wallis analysis of variance).

Reticulocytes were higher at 10 µg (day 15, 18% ± 13%; \( P < .001 \)) and 15 µg (day 13, 13% ± 14%; \( P < .05 \); and day 15, 14% ± 9%; \( P < .01 \)) rhIL-3 compared with the control cycles (day 13, 6% ± 5%; day 15, 8% ± 5%).

Documented urinary tract infections requiring IV antibiotic treatment occurred in two patients during the first IV
administered rhIL-3 cycle (5 and 10 μg/kg). A herpes simplex type I infection was observed during one rhIL-3 cycle (10 μg/kg) and three control cycles. None of the patients was hospitalized because of neutropenic fever in either the rhIL-3 cycles or the control cycles.

Chemotherapy postponement due to prolonged myelotoxicity was necessary in 22 of 45 control cycles and in 2 of 49 cycles (one patient not evaluable due to tumor progression in cycle 1) with rhIL-3 (P < .001, χ² test). Postponement was necessary in only one patient at 1 μg after cycles 1 and 3. One patient at the 1 μg/kg dose was taken off study after cycle 3 because of insufficient BM recovery. Because of tumor progression, three patients (two at 1 μg, one at 5 μg) were taken off study after cycle 5 and one patient (5 μg) after 21 days in cycle 1.

rhIL-3 administration did not result in elevation of IL-6 plasma levels, whereas slight increases in TNF-α plasma levels occurred only on the last day of rhIL-3 administration at the 5 to 15 μg/kg doses (median values, day 11, cycle 3: 1 μg, 8 ng/L; 5 μg, 19 ng/L; 10 μg, 15 ng/L; 15 μg, 27 ng/L). CRP and SAA plasma levels were only slightly elevated at the 10 μg/kg dose on the last day of rhIL-3 treatment (median value, day 11, cycle 3: CRP, 15 mg/L; SAA, 12 mg/L).

Fifty-two cycles with rhIL-3 (1 μg/kg, 12 cycles; 5 μg/kg, 13 cycles; 10 μg/kg, 15 cycles; and 15 μg/kg, 12 cycles) were evaluable for toxicity (Table 2). The most frequently observed side effects were fever WHO grade I-II and headache. Both symptoms were rhIL-3 dose-dependent and usually responded to acetaminophen (maximum 3 g/d). At 15 μg/kg, headache became dose-limiting in two patients during IV administration in cycles 1 and 3, respectively. rhIL-3 administration in these patients was discontinued on days 7 and 8, respectively. More than 50% of the patients experienced flu-like symptoms at 5 to 15 μg. A hemorrhagic rash (7 cycles) on the groins, the axillae, and the lower extremities usually occurred on days 8 or 9, a time point at which the platelet counts still were above 50 × 10⁹/L in all patients, and disappeared after discontinuation of rhIL-3. Local redness or infiltrates at the SC injection site were noticed in a minority of the cycles (11 of 32). Thrombophlebitis during IV rhIL-3 occurred in 9 of 20 cycles; however, this was not rhIL-3 dose-dependent. Facial erythema, starting 1 to 6 hours after rhIL-3 administration and lasting from hours to days, occurred at the 5 to 15 μg/kg dose steps, especially during the first days of treatment, and appeared to be dose-dependent in the patients treated IV. One patient at the 5 μg/kg dose experienced flushing in cycles 3 and 5 on the first day of SC administra-
tation. Flushing occurred once within 15 to 30 minutes after rhIL-3 and rapidly disappeared within 10 to 15 minutes. Peripheral basophil counts and urinary histamine metabolite levels at that time were not elevated in this patient. Moreover, rhIL-3 administration did not increase urinary histamine metabolite levels in any of the patients.

Two patients at the 1 µg/kg/d dose step had elevated liver function enzymes at entry of the study. One patient refused further treatment with rhIL-3 after chemotherapy, rhIL-3 could be safely administered to patients not treated with chemotherapy. The toxicity profile and incidence of the described side effects of SC rhIL-3 after chemotherapy were almost identical to the profile reported by others in patients not treated with chemotherapy. Liver toxicity did not appear to be clearly related to rhIL-3 administration. Our observation of flushing occurring only after the first rhIL-3 injection and the decreasing frequency of facial erythema during rhIL-3 demonstrates a certain degree of tachyphylaxis. Because urine histamine metabolite levels did not increase during rhIL-3 administration, histamine release from basophils was most probably not the cause of the side effects. Preclinical trials and in vitro studies showed an rhIL-3-related histamine release from basophils, but other clinical trials also demonstrated no increase of histamine release from basophils. Data on side effects of rhIL-3 administered IV are limited. Ganser et al observed transient acrocyanosis and chills in all three patients treated with 125 µg/m²/d as IV bolus. Kurzrock et al administered rhIL-3 (30 to 1,000 µg/m²/d) by a daily 4-hour IV infusion for 28 days to patients with BM failure. Preclinical trials and in vitro studies showed an rhIL-3-related histamine release from basophils, but other clinical trials also demonstrated no increase of histamine release from basophils. Data on side effects of rhIL-3 administered IV are limited. Ganser et al observed transient acrocyanosis and chills in all three patients treated with 125 µg/m²/d as IV bolus. Kurzrock et al administered rhIL-3 (30 to 1,000 µg/m²/d) by a daily 4-hour IV infusion for 28 days to patients with BM failure.

In their study, patients at all dose levels were febrile and headache was dose-related, but usually controlled with acetaminophen or codeine. rhIL-3 at 500 µg/m² was discontinued because of severe headache, nausea, and vomiting in one patient and because of recurrent urticaria in another.

rhIL-3 demonstrated a multilineage hematopoietic response after chemotherapy with increases in leukocytes, platelets, and, to a lesser extent, reticulocytes compared with the control cycles. It is possible that the degree of

### Table 1. Platelet Counts (x10⁹/L) on Days 1 and 22 in Patients at 10 µg/kg/d

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<th>4</th>
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<td>370</td>
<td>296</td>
<td>236</td>
<td>398</td>
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</table>

### Table 2. rhIL-3-Related Toxicity During SC or IV Administration

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<tr>
<th>SC</th>
<th>IV</th>
<th>SC</th>
<th>IV</th>
<th>SC</th>
<th>IV</th>
<th>SC</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>8</td>
<td>5</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Fever WHO grade I-II</td>
<td>1 (14)</td>
<td>2 (40)</td>
<td>3 (38)</td>
<td>5 (100)</td>
<td>6 (60)</td>
<td>5 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td>2 (25)</td>
<td>1 (20)</td>
<td>9 (90)</td>
<td>5 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Flu-like symptoms/chills</td>
<td>3 (43)</td>
<td></td>
<td>5 (63)</td>
<td>1 (20)</td>
<td>6 (60)</td>
<td>2 (40)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Flushing</td>
<td></td>
<td></td>
<td>2 (25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facial erythema</td>
<td></td>
<td>1 (13)</td>
<td></td>
<td>2 (20)</td>
<td>1 (20)</td>
<td>1 (14)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (14)</td>
<td>2 (25)</td>
<td></td>
<td>5 (50)</td>
<td>3 (60)</td>
<td></td>
<td>3 (60)</td>
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<tr>
<td>Rash</td>
<td></td>
<td>1 (13)</td>
<td>2 (40)</td>
<td>1 (10)</td>
<td>1 (20)</td>
<td>2 (67)†</td>
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<tr>
<td>Urticaria</td>
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<td>2 (25)</td>
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<td></td>
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Incidence of thrombophlebitis during IV rhIL-3 and local reaction after SC rhIL-3 are described in the text. Percentages are in parentheses.

*Two patients off study due to severe headache.
†Only 3 cycles evaluable for rash.
cytopenia in the control cycles was slightly influenced by administration of rhIL-3 in the prior cycle. However, because all control cycles were preceded by rhIL-3 cycle, such an effect could not be demonstrated. rhIL-3 at doses from 5 to 15 μg/kg/d demonstrated a clear effect on the neutrophil counts. The increase in neutrophil counts was most evident during the recovery phase, 1 week after stopping rhIL-3 treatment. This finding is of clinical importance, as it demonstrates that rhIL-3 can reduce the duration of neutropenia after chemotherapy and could diminish the risk of infectious complications. None of the rhIL-3 dose steps demonstrated a clear effect on the neutrophil nadir counts. The early effects on the neutrophil counts after 3 days of rhIL-3 treatment at the higher dose steps suggest a mobilization of neutrophils from the BM or marginal pool. A similar early response to rhIL-3 was observed in some patients with aplastic anemia.21 rhIL-3 also increased the monocyte, eosinophil, basophil, and lymphocyte counts at the 5 to 15 μg doses. A similar multilineage effect of rhIL-3 has been demonstrated in previous clinical trials.10 However, we could not demonstrate differences in effects on leukocyte counts between the 5, 10, and 15 μg dose steps.

Of interest is the effect of rhIL-3 on the platelet counts. At all rhIL-3 dose steps, platelets recovered faster in comparison with the control cycles. Because there was no significant difference in creatinine clearance between the rhIL-3 dose steps, a comparison of the rhIL-3 effects on the platelet counts at the different dose steps could be made.31 Although no clear protection of platelet nadir could be demonstrated, there was a tendency towards less platelet transfusions in cycles with rhIL-3. At the 10 and 15 μg/kg doses, no platelet transfusions were necessary. However, we could not demonstrate differences in effects on platelet recovery between the different rhIL-3 dose steps. rhIL-3 at doses of 60 to 500 μg/m²/d administered SC to cancer patients with normal hematopoiesis increased the peripheral neutrophil, monocyte, eosinophil, lymphocytes, and platelet counts in a dose-related manner,19 whereas the platelet counts started to increase earlier at higher dosages with counts continuing to increase for 1 week after discontinuation of rhIL-3. The missing dose-related increase in leukocyte and platelet counts at the higher rhIL-3 dose levels may be related to the small groups of patients or the duration of rhIL-3 administration. In the study by Ganser et al, the most pronounced increase in leukocyte and platelet counts occurred in the second week of rhIL-3 treatment.19 Studies with rhIL-3 in patients with BM failure, aplastic anemia, or myelodysplastic syndrome seem to demonstrate that the magnitude of effect of rhIL-3 on the leukocyte and platelet counts is closely related to the remaining BM function.19,22

rhIL-3 can stimulate proliferation of some solid tumor cells in vitro.32-34 In addition, it was recently demonstrated that a small cell lung carcinoma cell line possessed IL-3 receptors.34 However, it appears that CSFs can stimulate in vitro proliferation of only a minority of tumor cell lines and tumors.34-36 Although in our patients there was no evidence for an adverse effect of rhIL-3 on tumor growth, the group was too small to draw any final conclusions concerning this possible effect.

In several clinical studies it was shown that rhGM-CSF induced increases in TNF-α, IL-6, CRP, and/or SAA serum levels in vivo.5,7,28 Because IL-3 is an earlier acting hematopoietic growth factor than GM-CSF, a similar or more pronounced effect of rhIL-3 on these cytokine plasma levels appeared possible. Effects of rhIL-3 on cytokine plasma levels were limited and indicated that rhIL-3 does not induce an acute phase response in patients treated with chemotherapy. Oster et al reported slight increases in CRP serum levels after IV bolus rhIL-3 and, in some patients, slight increases in IL-6 serum levels.39

The present study demonstrated that rhIL-3 up to 10 μg/kg/d can be safely administered to patients treated with chemotherapy. The MTD in this study was 10 μg/kg/d, as severe headache was dose-limiting at 15 μg. Of interest was the similar efficacy of SC and IV rhIL-3 administration as, for a wider application of rhIL-3, use on an outpatient basis favors the SC pathway. rhIL-3 at doses of 5 to 15 μg/kg demonstrated a multilineage effect on hematopoiesis. Although both GM-CSF and G-CSF can reduce chemotherapy-related neutropenia,5,9 the effect of GM-CSF on platelet counts is inconsistent,7,10 whereas G-CSF does not affect the platelet recovery at all.50 Therefore, rhIL-3 appears to be an interesting CSF for attempting to reduce chemotherapy-related neutropenia and thrombocytopenia, thus probably diminishing the risk of infectious complications and bleeding.

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