Thrombopoietic Effects and Toxicity of Interleukin-6 in Patients With Ovarian Cancer Before and After Chemotherapy: A Multicentric Placebo-Controlled, Randomized Phase Ib Study


Recombinant human interleukin-6 (IL-6) has previously been shown to increase platelet counts in normal and sublethally irradiated mice, dogs, and primates. To assess its tolerance and efficacy in clinical use, we performed a randomized phase Ib study in patients with ovarian carcinoma. IL-6 was administered during an initial 7-day cycle before any chemotherapy. Beginning 7 days later, six cycles of chemotherapy containing carboplatin were administered every 3 weeks. During chemotherapy cycles 2 to 6, IL-6 was administered from day 4 through day 17 at escalating dose levels from 0.5 to 10 µg/kg/d. At each dose level, three patients received IL-6 and one patient received a placebo. During the chemotherapy cycle of IL-6, a dose-dependent increase in platelet count was observed from day 12 to 15 and was maximal on day 15 (r = 77; P < .01). The median ploidy of bone marrow megakaryocytes shifted from 16 N to 32 N after 7 days of the initial prechemotherapy IL-6 administration. Dose-dependent increases in C-reactive protein (CRP) and fibrinogen levels were observed on day 8 (P < .0001 for both). A significant decrease in hemoglobin level occurred rapidly after initiation of IL-6 therapy and was maximal on day 8 (P < .001). When given after chemotherapy, IL-6 accelerated platelet recovery after chemotherapy cycles 2 to 6. Postponements of scheduled chemotherapy due to thrombocytopenia were less frequent in patients treated with IL-6. No difference in either neutrophils or peripheral blood progenitor assays was observed during or after IL-6 treatment. Toxicity of IL-6 appeared mild and was not dose-limiting up to 10 µg/kg/d. Systemic symptoms such as fever, headache, and myalgia were the main side effects and were easily relieved by acetaminophen administration. No biologic toxicity was observed. The data indicate that IL-6 is a well-tolerated cytokine and capable of accelerating platelet recovery in patients receiving chemotherapy.

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Thrombocytopenia remains a frequent source of morbidity due to antineoplastic agents and often limits dose intensity. This toxicity is most severe with directly myelotoxic agents such as carboplatin. A variety of hematopoietic growth factors have already been studied in clinical trials and have been shown to promote proliferation and differentiation of megakaryocytopoiesis in vitro, including interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin (Epo). However, GM-CSF and Epo have no significant effect on thrombopoiesis in vivo. In a number of clinical trials, IL-3 appeared to reduce chemotherapy-induced thrombocytopenia, but this effect was modest and the toxicity of IL-3 was not negligible.

Interleukin-6 (IL-6) is a pleiotropic cytokine involved in hematopoiesis, regulating immune responses, and inducing acute phase reactants. It is produced by a number of cell types, including leukocytes, endothelial cells treated with various inducers, and fibroblasts stimulated with IL-1 or tumor necrosis factor. In addition, IL-6 is an effective hematopoietic growth factor. In vitro and in animal models, it accelerates and enhances blast cell colony formation and together with IL-3 and GM-CSF potentiates the formation of multilineage granulocyte and macrophage colonies. Furthermore, IL-6 is instrumental in megakaryocytic differentiation by inducing polyploidization and maturation of megakaryocytes. This effect leads to increase in cell size, a shift of cell ploidy toward higher values, and increased platelet production. There is also a modest increase in megakaryocyte numbers when IL-6 is coadministered with IL-3 to animals in vivo or when it is present in high dose in culture medium in vitro. IL-6 is primarily a megakaryocyte differentiation factor and not a megakaryocyte colony-stimulating factor.

In preclinical studies, IL-6 significantly reduced radiotherapy- or chemotherapy-induced thrombocytopenia and accelerated platelet recovery in mice, dogs, and primates. However, the applicability of IL-6 as a therapeutic agent to reduce chemotherapy-induced thrombocytopenia is still to be demonstrated. In this phase Ib study, we investigated the effectiveness and toxicity of IL-6 in stimulating platelet production before and after carboplatin-containing chemotherapy in patients with advanced ovarian carcinoma.

PATIENTS AND METHODS

Patient selection. Adult patients with histologically documented ovarian cancer FIGO (International Federation of Gynaecology and Obstetrics) stage IC, II, III, or IV were eligible for study if they fulfilled the following criteria: an interval of at least 2 weeks since operation, a minimum life expectancy of 3 months, a performance status greater than 60 using the Karnofsky Index, a granulocyte count greater than 2 × 10^9/L, a platelet count greater than 100 × 10^9/L, a serum creatinine level less than 1.3 mg/100 mL, and a creatinine clearance rate greater than 80 mL/min, and a serum bilirubin level less than 1.5 times normal value. Patients who had received prior
chemotherapy or radiotherapy and those with concomitant or prior malignancy other than excised basal cell carcinoma of the skin or in situ cervical carcinoma were excluded. The protocol study was approved by the Institutional Review Board for Human Experimentation (Catholic University of Louvain Medical School, Brussels, Belgium), and witnessed verbal informed consent was obtained from patients before IL-6 therapy was begun.

**IL-6 and chemotherapy.** *Escherichia coli*-derived, recombinant human IL-6 was supplied by Sandoz (Basel, Switzerland). Lyophilized IL-6 was reconstituted in 1 mL of sterile water. IL-6 or placebo was administered by intravenous (IV) infusion within the first 24 hours, subcutaneously from day 2 to 7 of the prechemotherapy cycle, and subcutaneously on days 4 to 17 of chemotherapy cycles 2 to 6. Chemotherapy consisted of six cycles of carboplatin (400 mg/m²) and cyclophosphamide (600 mg/m²) administered together once every 3 weeks.

**Study design.** The present phase Ib study was a multicenter, placebo-controlled, randomized trial in which patients were expected to receive six cycles of IL-6 or placebo. To monitor the safety of IL-6 without intercurrent chemotherapy and to study its biologic activities, IL-6 or placebo was administered alone for 7 days. Escalating dose levels of 0.5, 1, 2.5, 5, and 10 μg/kg/d of IL-6 were examined with four or five patients per dose level (three receiving WHO toxicity grade 4 (except alopecia) or any other serious adverse event believed to be due to a given dose of IL-6, no further patient received six cycles of IL-6 or placebo. To monitor the safety of prechemotherapy IL-6 administration and once per week during each chemotherapy cycle at the same daily dosage as during the prechemotherapy IL-6 cycle. Serial determinations of vital signs as well as body weight and general physical examination were performed regularly, and patients were assessed according to World Health Organization (WHO) criteria. If two patients experienced WHO toxicity grade 4 (except alopecia) or any other serious adverse event believed to be due to a given dose of IL-6, no further patient received IL-6 at that or any higher dose. Complete blood cell counts were performed on days 1, 2, 3, 5, 8, 10, and 12 of the prechemotherapy IL-6 administration and on days 1, 4, 8, 10, 12, 15, 17, 19, and 22 of each chemotherapy cycle. Serum electrolytes as well as liver and renal functions were measured on days 1, 3, 8, and 15 of the prechemotherapy IL-6 administration and once per week during each chemotherapy cycle. Acute phase proteins and coagulation profile were performed once per week during the prechemotherapy cycle and then once before each chemotherapy cycle. Urine analysis was performed once weekly during all cycles. Complete tumor staging and laboratory data were analyzed by standard statistical methods. All results were expressed as the mean ± SEM. Two-sided t-tests or paired t-tests (Student’s) and χ² tests were applied at a significance level of P = .05 without adjustment for multiple testing.

**RESULTS**

**Patient characteristics.** Twenty-two patients with a median age of 54 years (range, 29 to 64 years) entered the study between October 1991 and March 1994. On presentation, two patients had ovarian carcinoma stage IC; three, stage II; 16, stage III; and one, stage IV. All patients were assessable for the side effects and hematologic effects of IL-6 during the prechemotherapy cycle. During chemotherapy cycles, 1 patient died due to progression after cycle 2; 2 patients were

<table>
<thead>
<tr>
<th>Dose of IL-6 (μg/kg/d)</th>
<th>Prechemotherapy</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
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<td>0</td>
<td>7</td>
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excluded because of progressive disease after cycles 3 and 4, respectively; and 1 refused to continue after cycle 4. One patient was excluded on the first day of chemotherapy because of pulmonary embolism. All chemotherapy cycles before exclusion were assessable for these patients, and all cycles were assessable for the other patients. The numbers of patients assessable at each dose level are presented in Table 1.

Side effects of IL-6. To monitor the toxicity of IL-6 without concurrent chemotherapy, side effects during the prechemotherapy cycle were independently analyzed (Table 2). WHO grade I-II fever was the most frequently observed side effect and was consistent in patients who received IL-6 doses of 5 μg/kg/d or more. One patient treated with IL-6 2.5 μg/kg/d presented with WHO grade III fever. Temperature rose most frequently in the first 24 hours of IL-6 administration and persisted throughout all the prechemotherapy cycle. Other side effects included WHO grade I-II headache without signs of meningeal irritation, WHO grade I-II cutaneous side effects, and WHO grade I myalgia. Cutaneous side effects consisted of local erythema and sometimes pruritus at the site of IL-6 injection. Fever, headache, and myalgia responded well to acetaminophen administration, invariably disappeared following cessation of IL-6, and did not necessitate premature termination of IL-6. Asymptomatic mild increase in alkaline phosphatase and transaminases on day 8 of the prechemotherapy cycle (2 times normal value) was observed in one patient treated with IL-6 0.5 μg/kg/d. No change in serum creatinine level, coagulation parameters, or cardiac dysrhythmia were observed. The toxicity of IL-6 administered after chemotherapy was milder than toxicity observed during the prechemotherapy infusion.

Hematologic effects before any chemotherapy. After the prechemotherapy infusion of IL-6, a statistically significant increase in platelet counts was observed in patients who received 2.5 to 10 μg/kg/d of IL-6. This increase was maximal at day 15. Platelet counts of these patients at day 15 were significantly higher compared with both their baseline mean ± SEM (681 × 10^9/L ± 55 × 10^9/L v 356 × 10^9/L ± 26 × 10^9/L; P < .001, t-test) and platelet counts of placebo patients at day 15 (681 × 10^9/L ± 55 × 10^9/L v 314 × 10^9/L ± 40 × 10^9/L; P < .001, t-test). This increase appeared to be dose-dependent (r = .77; P < .001; Fig 1). No significant change in platelet counts was observed during the 7 days of concomitant IL-6 administration. The median ploidy of megakaryocytes, measured in four patients (1 patient treated with IL-6 1 μg/kg/d, 2 with 2.5 μg/kg/d, and 1 with 5 μg/kg/d), shifted from 16 N to 32 N after 7 days of IL-6 administration (Fig 2).

No significant change was observed in either total white blood cell counts or differential counts during or after IL-6 administration except for eosinophils. Eosinophil counts decreased significantly from day 2 to 8 of IL-6 administration and returned to baseline value on day 12.

A statistically significant decrease in hemoglobin and red blood cells (RBCs) occurred rapidly, within the first 24 hours after initiation of IL-6 therapy, and was maximal on the last day of IL-6 administration, day 8. On that day, the mean hemoglobin level of patients treated with IL-6 2.5 to 10 μg/kg/d was 9.4 ± 0.4 g/dL compared with their mean baseline value of 12.2 ± 0.4 g/dL (P < .001; t-test). At 10 days after the end of IL-6 administration, hemoglobin levels had returned to baseline value. This decrease in hemoglobin was not accompanied by signs of hemolysis nor changes in mean corpuscular volume.

No significant change was observed in PB CFU-GM-, BFU-E- or CFU-GEMM-derived colonies in patients

Table 2. Side Effects of IL-6 Before Administration of Chemotherapy

<table>
<thead>
<tr>
<th>IL-6 Dose (μg/kg/d)</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
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<tbody>
<tr>
<td>No. of patients</td>
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<td>3</td>
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<tr>
<td>Fever</td>
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<tr>
<td>WHO grade I</td>
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<tr>
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<td></td>
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<tr>
<td>Headache WHO grade I-II</td>
<td>1 (13)</td>
<td>2 (66)</td>
<td>2 (66)</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous WHO grade I-II</td>
<td>2 (27)</td>
<td>2 (66)</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td></td>
</tr>
<tr>
<td>Myalgia WHO grade I</td>
<td>1 (1)</td>
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</table>

Data are numbers of patients, with percentages given in parentheses.
therapy administration of 11-6. Four patients were analyzed (one patient received 1 µg/kg/d, two received 2.5 µg/kg/d, and one received 5 µg/kg/d).

Hematologic recovery after chemotherapy. Platelet nadirs were observed on day 15 of chemotherapy cycles, and the depths of the nadirs were not significantly different in cycle 1 compared with cycle 2 in patients treated at all IL-6 levels. However, on days 17, 19, and 22 of the second chemotherapy cycle, recovery of platelet counts was faster as compared with days 17, 19, and 22 of the first chemotherapy cycle for patients treated with IL-6 2.5 to 10 µg/kg/d (142 ± 10^9/L ± 10 x 10^9/L v 64 ± 10^9/L ± 11 x 10^9/L at day 17, 260 ± 10^9/L ± 40 x 10^9/L v 92 ± 10^9/L ± 17 x 10^9/L at day 19, 448 ± 10^9/L ± 74 x 10^9/L v 192 ± 10^9/L ± 24 x 10^9/L at day 22, P = .003, .002, and .005, respectively; t-test; Fig 3). In those same patients, on days 19 and 22 of the second chemotherapy cycle, platelet counts were also higher as compared with placebo patients (260 ± 10^9/

L ± 40 x 10^9/L v 75 ± 10^9/L ± 36 x 10^9/L at day 19, 448 x 10^9/L v 74 x 10^9/L v 165 ± 10^9/L ± 36 x 10^9/L at day 22; P = .03 for both; Fig 4). A similar difference was observed during all cycles of chemotherapy, but statistical analysis was not performed on the last two cycles due to the low number of values after exclusion of some patients after the third chemotherapy cycle (see Patient characteristics).

Postponement of chemotherapy because of myelotoxicity (neutrophil count less than 1.5 x 10^9/L and/or platelet count less than 100 x 10^9/L) was necessary in 25 of 36 (69%) chemotherapy cycles for patients treated with placebo and IL-6 0.5 µg/kg/d. In comparison, 25 of 58 chemotherapy cycles (43%) were postponed among patients treated with IL-6 0.5 µg/kg/d (P = .024, χ²). Among these postponements, 10 of 25 were due to thrombocytopenia for patients treated with placebo and IL-6 0.5 µg/kg/d compared with 3 of 25 for patients treated with IL-6 ≥1 µg/kg/d (P = .05, χ²).

No difference in neutrophil recovery was observed during chemotherapy in patients treated at all IL-6 levels. Likewise, there was no difference in RBC transfusion requirements in IL-6 patients compared with placebo patients during chemotherapy (P = .97, χ²).

Induction of acute-phase proteins. During the prechemotherapy cycle, C-reactive protein (CRP) and fibrinogen levels increased dramatically after 1 week of IL-6 administration. For patients treated with 0.5 to IL-6 10 µg/kg/d, the CRP level increased from a baseline mean value of 0.65 ± .33 mg/dl to 16.3 ± 2.6 mg/dl at day 8 (P < .0001, t-test). Fibrinogen increased from 306 ± 19 mg/dl to 713 ± 70 mg/dl (P < .0001, t-test) on the same days. These increases appeared at even low levels of IL-6 administered and were dose-dependent (r = .89, P < .0001 for CRP and r = .82, P < .0001 for fibrinogen).

DISCUSSION

The primary purpose of this study was to determine the optimal dose and attendant toxicity of IL-6 administered...
alone and in conjunction with combination chemotherapy. As administered in this trial, IL-6 was generally well tolerated. No side effect was dose-limiting. Systemic symptoms such as fever, headache, and myalgias were the main side effects and were easily relieved by administration of acetaminophen. These symptoms are attributed to immune and acute phase responses to IL-6 and were similar to those previously described. Additionally, cutaneous side effects consisting of a local reaction at the injection site of IL-6 were observed. Cardiovascular toxicity (atrial fibrillation) reported by Weber et al in two patients who received IL-6 at 30 µg/kg/d was not observed in our study. One patient treated with IL-6 0.5 µg/kg/d presented with asymptomatic mild increase in alkaline phosphatase and transaminase (2 times normal value). These changes could reflect the physiologic effect of IL-6 on hepatocytes. More severe hepatotoxicity was observed in one patient treated with 30 µg/kg by Weber et al. No change in either creatinine or in coagulation parameter was observed.

IL-6 administered for 1 week before chemotherapy resulted in a dose-dependent increase in the platelet count, increasing up to threefold and reaching a maximum on day 15. In four patients in whom it was measured, the median ploidy of megakaryocytes shifted from 16 N to 32 N after 1 week of IL-6 administration. Stimulation of human megakaryocyte progenitors takes place at both an early and a late stage of differentiation. In early steps of hematopoietic differentiation, several growth factors, including IL-3 and GM-CSF, are able to induce proliferation and differentiation of the committed progenitor but are not specific for the megakaryocytic lineage. IL-6 is one of the main stimulators at the late stages of megakaryocytic differentiation. In vitro, IL-6 increases ploidization and size of individual megakaryocytes. Moreover, at high dose levels, IL-6 acts synergistically with IL-3 in vitro to stimulate megakaryocytic proliferation and differentiation at early steps. Preclinical studies in healthy primates have shown that in vivo administration of IL-6 increased platelet production and induced a right shift in megakaryocytic DNA ploidy. In the present clinical study, we found similar stimulation of platelet production in the prechemotherapy cycle. The time to obtain maximal effect on platelet production may reflect the time necessary to increase megakaryocytic ploidy and size in response to IL-6, which in turn causes an increased efflux of platelets from the marrow. In fact, the shift of megakaryocyte ploidy appeared 1 week before maximal peripheral platelet counts. This delay is similar to that observed in primates and by Weber et al in patients with advanced malignancies. Nevertheless, there is no definitive explanation for this delay in IL-6-induced increases in platelet counts. In our study, IL-6 had no effect on white blood cells. In animals, significant elevation in white blood cell count has been observed only with higher doses of IL-6 and could be an effect on early progenitor cells. An unexplained statistically significant decrease in eosinophil counts was observed during IL-6 administration. No significant change of PB progenitor cells (CFU-GM, BFU-E, and CFU-GEMM) was observed during or after IL-6 administration. Because a PB CFU-Mk assay was not performed, we cannot definitely exclude that IL-6 alone or in combination with other cytokines might be useful in mobilization of progenitor cells into the PB.

A significant decrease in hemoglobin levels and RBCs occurred within the first 24 hours after IL-6 initiation and was maximal on day 8. After discontinuing IL-6, recovery occurred within 10 days. The pathogenesis of this observation is not clear. In our patients, as in those included in other studies, no laboratory signs of hemolysis (haptoglobin, lactate dehydrogenase, and bilirubin levels not modified) or changes in mean corpuscular volume were observed. In animal studies, no toxic effects of IL-6 on erythroid precursors were seen in BM samples. Possibly, similar mechanisms are involved, as in the anemia of chronic disease attributable to alterations in iron metabolism (excessive sequestration of iron and iron-binding protein), and/or increased RBC sequestration into the hepatic and splenic reticuloendothelial system may occur. These mechanisms may be induced by acute phase reactants. No data are as yet available on iron-binding protein after administration of IL-6. Recently, it has been proposed that IL-6-associated anemia is primarily caused by an increase in plasma volume without an RBC mass decrease. Whatever the mechanism during chemotherapy may be, this effect appeared to be of no clinical importance, as the need for RBC transfusion was not increased in IL-6 patients as compared with placebo patients.

Dose-dependent increases in fibrinogen and CRP appeared during IL-6 treatment. In vitro evidence for IL-6 as a major inducer of acute phase proteins in humans has come from studies with human hepatocytes in primary culture, including CRP, ceruloplasmin, haptoglobin, fibrinogen, α1-acid glycoprotein, α1-antitrypsin, antichymotrypsin, and complement factor B. These observations have been confirmed in preclinical studies in and in humans. In the present study, the increase in IL-6-induced acute phase proteins did not appear to be hepatotoxic.

As in irradiated monkeys, in which IL-6 significantly reduced the degree of thrombocytopenia and shortened platelet recovery, the present study indicates that at dose levels of 2.5 to 10 µg/kg/d, IL-6 administration during chemotherapy resulted in a faster platelet recovery at day 17 of chemotherapy cycle 2 compared with the corresponding day of chemotherapy cycle 1. The study was designed to allow comparison of platelet kinetics in the same patients treated with or without IL-6 (cycle 2 v cycle 1) as well as to compare IL-6 patients to placebo patients during the same cycle. In both cases, platelet recovery was accelerated with IL-6. The time delay to the observed effect on maximal platelet stimulation during chemotherapy (from day 13 after IL-6 initiation) is similar to that observed in prechemotherapy IL-6 administration. The total number of chemotherapy postponements caused by myelotoxicity was lower in patients treated with IL-6, and among these, the percentage of postponements due to thrombocytopenia was also reduced significantly.

Other hematopoietic growth factors, including IL-3, leukemia inhibitory factor, and IL-11, have been shown to act on the megakaryocytic lineage. When given in vivo, most of these factors act very progressively and have the potential
disadvantage of causing unwanted effects on a variety of other lineages. The recently cloned c-mpl ligand appears to have selective actions on megakaryocyte proliferation and differentiation. Administration of c-mpl ligand to mice induced a fourfold increase in platelet counts within 4 days. Combined with other cytokines, the c-mpl ligand can further increase its thrombopoietic activity. The optimal promotion of platelet recovery after high-dose chemotherapy might be achieved by a combination of growth factors that remains to be determined.

In conclusion, the present study shows that IL-6 in doses up to 10 μg/kg/d can be safely administered in patients receiving chemotherapy. IL-6 has a stimulatory effect on thrombopoiesis before administration of chemotherapy and accelerates platelet recovery after chemotherapy. The observed reduction of chemotherapy delays caused by thrombocytopenia should allow patients to receive planned chemotherapy on schedule and at the full dose. This, in turn, might allow a higher dose intensity of the cytotoxic therapy, thereby possibly increasing the disease-free and overall survival rates of patients with advanced malignancies.

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Thrombopoietic effects and toxicity of interleukin-6 in patients with ovarian cancer before and after chemotherapy: a multicentric placebo-controlled, randomized phase Ib study

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