A Phase I Trial of Recombinant Human Interleukin-11 (Neumega rhIL-11 Growth Factor) in Women With Breast Cancer Receiving Chemotherapy

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We performed a phase I trial of recombinant human interleukin-11 (rhIL-11) in women with breast cancer. Cohorts of three to five women were accrued to five dosage levels of rhIL-11 (10, 25, 50, 75, and 100 μg/kg/d). rhIL-11 alone was administered by a daily subcutaneous injection for 14 days during a 28-day prechemotherapy "cycle 0." Patients (pts) subsequently received up to four 28-day cycles of cyclophosphamide (1,500 mg/m²) and doxorubicin (60 mg/m²) chemotherapy followed by rhIL-11 at their assigned dose (days 3 through 14). Sixteen pts (13 stage IV, 3 stage IIIB) were accrued to this study. Median age was 53 years and median Eastern Cooperative Oncology Group Performance Status was 0. A grade 3 neurologic event was seen in 1 pt at 100 μg/kg. Because of the degree of grade 2 constitutional symptoms (myalgias/arthralgias and fatigue) at 75 μg/kg, dose escalation was stopped and 75 μg/kg was the maximally tolerated dose. No other grade 3 or 4 adverse events related to rhIL-11 were seen. The administration of rhIL-11 was not associated with fever. Reversible grade 2 fatigue and myalgias/arthralgias were seen in all pts at 75 μg/kg. Weight gain of 3% to 5% associated with edema was seen at doses >10 μg/kg but a capillary leak syndrome was not seen. rhIL-11 alone was associated with a mean 76%, 93%, 108%, and 185% increase in platelet counts at doses of 10, 25, 50, and 75 μg/kg, respectively. No significant changes in leukocytes were seen. A mean 19% decrease in hematocrit was observed. Acute-phase proteins increased with treatment at all doses. Compared with patients at the 10 μg/kg dose, patients receiving doses ≥25 μg/kg experienced less thrombocytopenia in the first two cycles of chemotherapy. We conclude that rhIL-11 has thrombopoietic activity at all doses studied, is well tolerated at doses of 10, 25, and 50 μg/kg, and at doses ≥25 μg/kg has the potential to reduce chemotherapy-induced thrombocytopenia in this model.

THROMBOCYTOPENIA has become an increasing problem for cancer patients receiving chemotherapy. Because the use of the myeloid colony-stimulating factors (CSFs) has reduced the incidence of febrile neutropenia after standard-dose chemotherapy, the administration of more dose-intensive chemotherapy regimens has been pursued.[1] As a result, greater degrees of acute and prolonged thrombocytopenia are increasingly being observed. This has resulted in an increased utilization of platelet transfusions with the inherent increased risk of transfusion-related infectious complications. In addition, the quality of life of those patients requiring frequent blood counts and transfusions is impaired. Although the use of reinfused peripheral blood (PB) progenitor cells has reduced the degree of thrombocytopenia associated with high-dose chemotherapy, this technology is cumbersome and costly. No currently available hematopoietic growth factor routinely reduces the degree of thrombocytopenia secondary to cytotoxic chemotherapy in a manner similar to that of the myeloid CSFs.

Interleukin-11 (IL-11) is a pleiotropic hematopoietic growth factor initially detected in the conditioned medium derived from the immortalized primate bone marrow (BM) stromal cell line PU-34.[2] The activity of this agent was characterized by its stimulation of the proliferation of the IL-6–dependent plasmacytoma cell line, T1165. This effect was not eliminated by the addition of anti–IL-6 antibodies, showing that this was a unique factor. The human homologue of the IL-11 gene was isolated from a lung fibroblast cell line and encoded a 19-kD protein comprised of 178 amino acids. This gene is located on chromosome 19.[2]

In vitro, IL-11 synergizes with other hematopoietic growth factors (eg, IL-3 and c-*kit* ligand) promoting the proliferation of various classes of hematopoietic progenitor cells committed to a variety of lineages.[3-5] As a single agent, IL-11 induces the maturation of early megakaryocytes by increasing megakaryocyte size and ploidy.[6] In preclinical in vivo models, IL-11 stimulates platelet production in normal animals, including mice and nonhuman primates. This effect is dose-related and is characterized by increases in peripheral platelet counts, which peak approximately 14 to 21 days after initiation of administration.[7,8] Multilineage effects, including increases in reticulocytes and white blood cell (WBC) subsets, have been seen in several of these preclinical models.[9] After the administration of chemotherapy to mice, IL-11 significantly accelerates the multilineage recovery of hematopoiesis.[9] When IL-11 is administered in a murine transplant model, it demonstrates similar multilineage effects, accelerating the recovery of platelets, neutrophils, and reticulocytes.[10]

Based on its in vitro and in vivo preclinical thrombopoietic activity, we hypothesized that IL-11, having potential thrombopoietic activity and multilineage hematologic effects, would be an ideal hematopoietic growth factor to diminish the degree of chemotherapy-related thrombocytopenia. Our goal was to assess the safety and biologic properties of the recombinant protein (Neumega rhIL-11 growth factor; rhIL-11). In our study, rhIL-11 was administered to women with breast cancer both before and after dose-intensive chemo-

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therapy. We report that rhIL-11 is well tolerated at clinically relevant doses and has thrombopoietic activity in women with normal hematopoiesis. When administered after the administration of dose-intensive chemotherapy, rhIL-11 at doses of 25 to 75 μg/kg subcutaneously (SC) daily has the ability to attenuate the development of severe thrombocytopenia.

MATERIALS AND METHODS

Patient eligibility. Women with pathologically confirmed breast cancer that was either locally advanced (stage IIIB) or metastatic (stage IV) were eligible for the study if they met the following criteria: age 18 years or older; practicing an approved method of birth control with a negative Beta Human Chorionic Gonadotropin (β-HCG) pregnancy test (if appropriate); an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1; at least 4 weeks from prior adjuvant chemotherapy with complete recovery from all toxicity; adequate hepatic and renal function (total bilirubin level ≤2.0 mg/dL, blood urea nitrogen (BUN) ≤30 mg/dL, serum creatinine level ≤2.0 mg/dL); normal left ventricular ejection fraction (≥50% on radionuclide ejection fraction [RNEF]); no prior chemotherapy for metastatic disease; and no clinically significant cardiac or metabolic disease. Patients were required to be seronegative for human immunodeficiency virus and hepatitis B surface antigen.

Patients with a history of thrombo-embolic phenomena, prior doxorubicin exposure of >250 mg/m^2, those who were anticipated to require radiation therapy during the course of the study, had a contraindication to delaying chemotherapy for 4 weeks, or were receiving treatment with corticosteroids, aspirin, nonsteroidal anti-inflammatory agents, or anticoagulant drugs were excluded. We also excluded patients with a documented history of brain metastases or seizures, or other cancer within 5 years of study entry (with the exception of carcinoma in situ of the uterine cervix or surgically cured nonmelanoma skin cancer). Patients were also ineligible if they had received radiation therapy or surgery within 2 weeks before study entry, had undergone prior pelvic irradiation at any time, or were treated with any investigational agent or cytokine within 4 weeks of study entry. All patients were required to give written informed consent, and the protocol was approved by the Institutional Review Board of the Indiana University School of Medicine.

Study medication. *Escherichia coli*–derived, nonglycosylated rhIL-11 (Neumega rhIL-11 growth factor) was provided by Genetics Institute (Cambridge, MA). Vials containing 5 mg/mL of rhIL-11 in 1 mL of USP Sterile water for injection were used. Vials were used only once and then discarded. The specific activity of the rhIL-11 was determined by a bioassay on the basis of [^{3}H]-thymidine incorporation in a responsive cell line and was >0.6 × 10^6 U/mg. The study agent contained less than 1 ng of endotoxin by Limulus amoebocyte lysate assay Cyclophosphamide, doxorubicin, and Neupogen (Amgen Inc, Thousand Oaks, CA) (granulocyte colony-stimulating factor [G-CSF]) were obtained commercially.

Study design. The study schema is shown in Fig 1. In this open-label, nonrandomized phase I trial, 16 patients were enrolled between December 1992 and December 1993. Cohorts of three to five patients were accrued to each of four planned dose levels of rhIL-11 including 10, 25, 50, and 75 μg/kg/d. rhIL-11 was administered as a daily subcutaneous injection for 14 days followed by a 14-day washout period during a 28-day prechemotherapy safety period termed cycle 0. Patients were observed for 6 hours in the General Clinical Research Center at Indiana University Medical Center after each of the first three doses of rhIL-11 and continued to be treated as outpatients thereafter.

After completion of cycle 0, patients received up to four monthly cycles of chemotherapy consisting of cyclophosphamide 1,500 mg/m^2 and doxorubicin 60 mg/m^2 on the first day of each 28-day cycle. All patients received rhIL-11 at their assigned dose for 12 days (days 3 through 14) following the administration of chemotherapy. Any patient who experienced severe neutropenia defined as a febrile neutropenic event or an absolute neutrophil count ≤500 cells/μL for more than 5 days during cycles 1 or 2 were eligible to receive Neupogen at a dose of 5 μg/kg/d administered SC from day 3 through neutrophil recovery (absolute neutrophil count ≥2,000 cells/μL for 3 days) in cycles 3 and 4. There was no intrapatient dose escalation allowed. If at any time the platelet count increased to greater than 600,000/μL during rhIL-11 administration, rhIL-11 was discontinued during that cycle of therapy.

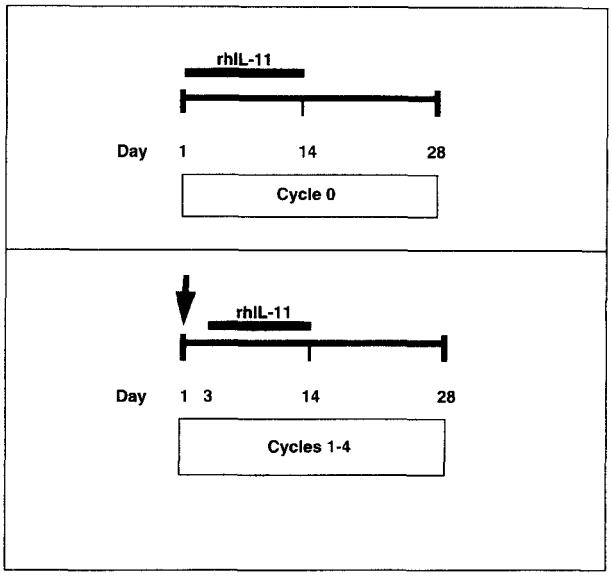

Fig 1. Study schema. Cohorts of at least three patients were accrued to each of the planned dose levels of rhIL-11. During the prechemotherapy phase termed cycle 0, rhIL-11 was administered by a daily SC injection for 14 consecutive days followed by 14 days of observation. Subsequently, patients received up to four monthly cycles of chemotherapy. Cyclophosphamide (1,500 mg/m^2) and doxorubicin (60 mg/m^2) were administered on day 1 of each cycle (dark arrow), followed by daily SC injections of rhIL-11 at their assigned dose for 12 days (days 3 through 14).

Dose escalation was based on adverse events seen in cycle 0 only and was allowed if none of the three patients at a given dose experienced grade 3 or greater adverse events in the first 14 days of IL-11 therapy. If one of the three patients experienced a serious adverse event, an additional two patients were added to that cohort. Dose-limiting toxicity (DLT) was defined as the dose which resulted in two or more patients with grade 3 or greater toxicity. The maximally tolerated dose (MTD) was defined as the dose level immediately below that which resulted in DLT. An additional three patients were allowed to be accrued to either the MTD or, in the absence of establishing an MTD, to a safe, biologically active dose. These additional patients did not receive rhIL-11 during cycle 0, and were treated only in cycles 1 through 4 of the study. Patients experiencing grade 3 or greater toxicity were removed from the study. All toxicities were graded according to the World Health Organization (WHO) common toxicity criteria.[11]

Evaluations. All patients underwent a thorough physical examination including vital signs and ECOG performance status before enrollment on the study. This evaluation was repeated at intervals throughout the study. An RNEF (MUGA scan) was performed before

Table 1. Characteristics of Patients

No. of patients	16
Median age (range)	53 (26-67)
Median ECOG PS (range)	0 (0-1)
Stage	
IIIB	3
IV	13
Menopausal status	
Premenopausal	4
Postmenopausal	12

enrollment and repeated after the second and fourth cycles of chemotherapy. A chest radiograph and electrocardiogram were obtained at baseline, after the completion of rhIL-11 administration in cycle 0 (day 15, cycle 0) and at the end of cycle 0 (day 28). Complete blood counts including a manual differential count, absolute reticulocyte count, and an automated quantitation of platelet size were obtained at baseline and three times per week during cycles 0 through 4. Patients who developed platelet counts ≥600,000/μL during cycle 0 underwent daily complete blood counts until the platelet count decreased to below this level. Urinalysis, coagulation profiles, serum chemistries, and serum levels of acute phase proteins (C-reactive protein, fibrinogen, and haptoglobin) were performed at baseline and at varying intervals during cycles 0 through 4.

BM aspirates and trephine biopsies for morphology, progenitor cell numbers, immunophenotyping, and megakaryocyte ploidy analysis were performed at baseline and after completion of rhIL-11 administration in cycle 0 (day 15, cycle 0).

Serum anti–IL-11 antibodies. Serum samples were evaluated for the development of anti–IL-11 antibodies by an enzyme-linked immunoabsorbent assay (ELISA). Serum samples were obtained at baseline, on day 15 of cycle 0, and before the start of each cycle of chemotherapy (cycles 1 through 4) and at the follow-up visit 4 weeks after the end of the last chemotherapy cycle.

Clinical response criteria. Tumor measurements were obtained at baseline, after completion of cycle 0, and after the second and fourth cycles of chemotherapy. Clinical response was evaluated by comparing tumor measurements obtained from radiographic or physical examination findings. Standard Eastern Cooperative Oncology Group breast cancer response criteria were used. Any patient who was found to have progressive disease at any time was removed from the study.

Statistical analysis. Dose-limiting criteria were defined by standard criteria based on the dose-escalation schema outlined above. Analysis of changes in serum chemistries and acute-phase proteins was performed using a two-sided Student's paired *t*-test. Results of hematologic parameters were reported as mean or median values. When appropriate, 95% confidence intervals were calculated and presented.

RESULTS

Patient characteristics. Sixteen patients with pathologically confirmed breast cancer (3 stage IIIB, 13 stage IV) were accrued to this phase I trial. Pretreatment characteristics and extent of disease/prior therapy are shown in Tables 1 and 2. All 16 were eligible for assessment of safety. Thirteen patients received rhIL-11 during cycle 0: 12 patients were enrolled in cohorts of 3 at the 10, 25, 50, and 75 μg/kg dose levels and 1 patient was enrolled at the 100 μg/kg dose level. After the completion of dose escalation, an additional three patients were accrued to the 50 μg/kg dose cohort to gain additional information about the effects of rhIL-11 at this dose after chemotherapy. The median age for patients treated on this study was 53 years (range, 26 to 67 years). Median ECOG performance status was 0 (range, 0 to 1). Nine patients had received prior adjuvant chemotherapy, including 4 who received prior radiation therapy (including patient number 008 at the 50 μg/kg dose who had previously received lumbar radiotherapy) and 5 who received prior hormonal therapy. Among the remaining patients, 2 had received prior radiotherapy and hormonal therapy, 2 had received prior hormonal therapy only, and 3 had received no prior therapy (all with stage IIIB disease).

IL-11 safety. Treatment with rhIL-11 was generally well tolerated. All side effects were reported regardless of their presumed relationship to rhIL-11 (Table 3). When the rhIL-11 alone cycle (cycle 0) is analyzed, the most common side effect is a therapy-related anemia that occurred in 11 of 11 patients who completed this phase of the trial. This anemia (~20% decrease in hematocrit) generally developed within 2 to 3 days of the initiation of IL-11 dosing and resolved over a 1- to 2-week period after completion of IL-11 therapy. Plasma volume studies performed in three patients showed increased plasma volumes (20%, 18%, and 21%) from days 2 to 15. No patient experienced significant blood loss or had any laboratory evidence of hemolysis. These increases in plasma volume are consistent with the development of the anemia.

The other most frequently reported side effects during cycle 0 included constitutional symptoms including arthralgias and myalgias, fatigue, nausea, and headache. Edema of the extremities was seen in all except one patient treated at doses ≥25 μg/kg and was primarily dependent in nature. The edema typically developed in the second week of rhIL-11 therapy and resolved after completion of the 14 days of treatment. No clinically significant fevers nor capillary leak syndromes were seen in patients receiving rhIL-11 during cycle 0. Although the majority of the side effects seen were mild-moderate (grade 1-2), the constitutional symptoms and edema were believed to be dose-related and were more intense at doses ≥50 μg/kg/d. When cycles of IL-11 administered after chemotherapy were evaluated, a similar toxicity profile was observed. No other unexpected adverse events were identified.

Five patients were removed from study for adverse events believed to be possibly or probably related to the study drug (Table 4). Only one patient was removed from study during cycle 0 for a severe adverse event (grade 3 or higher). This patient, the first treated at the 100-μg/kg dose level, experienced the onset of an expressive aphasia after three doses of rhIL-11. Computed tomographic (CT) scan of the head showed a 1- to 2-cm left Brocha's infarct and rhIL-11 therapy was discontinued. Her platelet count at the time of admission for the event was 220,000/μL and her fibrinogen level was 670 mg/dL. The patient underwent noninvasive doppler evaluation of her carotid arteries which demonstrated no clinically significant vaso-occlusive disease. With continued observation, the patient recovered to her baseline neurologic status. A second patient, with a history of hypertension, treated at the 50 μg/kg dose, was removed after

Table 2. Extent of Prior Therapy and Sites of Disease for Enrolled Patients

Pt. No.	Age	Stage	Site(s) of Disease	Prior Adj Chemo	Interval	Prior RT	Radiated Site(s)
1	56	IV	Bone	CMF	17 mo	Y	Chest Wall
2	67	IV	Liver	CMF	29 mo	N	N/A
3	59	IV	Liver	CAF/CMF	19 mo	N	N/A
4	54	IV	NED	CMF	12 mo	N	N/A
5	44	IIIB	Breast	None	N/A	N	N/A
6	36	IV	NED	None	N/A	N	N/A
7	52	IV	LN	CAF	100 mo	Y	Breast
8	60	IV	Bone/Chest Wall	None	N/A	Y	Lumbar spine
9	66	IIIB	Breast	None	N/A	N	N/A
10	37	IV	LN/Breast	CMF	12 mo	Y	Breast
11	54	IV	Pulmonary	CMF	34 mo	Y	Breast
12	64	IV	Pulmonary	None	N/A	N	N/A
13	67	IV	Pulmonary	None	N/A	Y	Breast
14	26	IIIB	Breast	None	N/A	N	N/A
15	48	IV	Chest Wall	CMF	7 mo	N	N/A
16	52	IV	NED	CMF	19 mo	N	N/A

Abbreviations: CMF, cyclophosphamide/methotrexate/fluorouracil; CAF, cyclophosphamide/doxorubicin/fluorouracil; Pt. No, patient number; Adj Chemo, adjuvant chemotherapy; RT, radiotherapy; NED, no evidence of disease; LN, lymph node; Y, yes; N, no; N/A, not applicable.

identification of a 1- to 2-cm intracerebral bleed at the time of the nadir of her blood counts following chemotherapy during cycle 1. This patient was admitted to the hospital with an episode of neutropenic fever and staphylococcal sepsis. Mental status changes were investigated with a CT scan of the head, which showed a small intracerebral bleed in the setting of chronic hypertensive cerebrovascular disease. The patient was removed from study and recovered completely with no significant sequelae from this event. The third patient, enrolled on the 75-μg/kg dose level, withdrew from the study after completion of cycle 1 because of what she perceived as unacceptable constitutional symptoms characterized by fatigue, arthralgias and myalgias, and edema. A final two patients were removed because of indwelling catheter-related complications of infection and thrombosis. Reasons for the removal of additional patients who failed to complete the entire four cycles of chemotherapy included: progression of disease (two patients), change in therapy to BM transplant (one patient), and neutropenic sepsis (one patient).

Table 3. Adverse Clinical Effects of rhIL-11 During Cycle 0 (All Grade 1 and 2)

	rhIL-11 (μg/kg/d)									
	10		25		50		75		100	
No. Assessable Pts	3		3		3		3		1	
WHO Grade	1	2	1	2	1	2	1	2	1	2
Anemia	3	0	1	2	1	2	0	2	0	0
Arthralgia/myalgia	3	0	1	0	2	0	1	1	0	0
Fatigue	3	0	1	1	1	2	0	3	0	0
Rhinorrhea	3	0	2	0	2	0	1	0	0	0
Nausea	2	0	1	0	1	0	1	1	0	0
Edema	1	0	3	0	1	1	2	1	1	0
Headache	2	0	0	0	1	1	1	1	0	0
Injection site rxn	3	0	2	1	0	0	1	1	1	0
Tachycardia	0	0	0	0	2	0	2	0	0	0

Abbreviation: rxn, reaction.

Serum anti–rhIL-11 antibodies. Anti–rhIL-11 antibody formation was assessed in all 16 patients. Two subjects were observed to demonstrate an anti–rhIL-11 response that was consistent with antibody formation as a result of product exposure. Of these two, one subject showed a positive response at the follow-up visit only, but had insufficient sample to confirm the authenticity of this titer. The other subject had a relatively low titer 14 days after product exposure, and although this subject did not have a detectable titer at the follow-up visit (26 days postexposure), there was a faint reactivity with the rhIL-11 band when this sample was analyzed by Western immunoblot analysis.

Hematologic effects of IL-11 during cycle 0. In the first course of therapy IL-11 was administered alone, 4 weeks before chemotherapy, to allow the evaluation of the safety as well as the hematologic and hematopoietic effects of IL-11. Treatment with IL-11 alone was associated with a dose-related increase in platelet counts. Increases of 76%, 93%, 108%, and 185% over baseline values were seen at the 10-, 25-, 50-, and 75-μg/kg/d dose levels, respectively (Fig 2A through D). This thrombocytosis was characterized by an initial slight transient decrease in platelets within the first 2 days of IL-11 therapy. Subsequently, platelet counts gradually increased to their peak levels over the 2 weeks of treatment. Maximal platelet counts occurred at a median of 18, 19, 16, and 14 days from the initiation of therapy for

Table 4. Reasons for Discontinuation of rhIL-11 Therapy

Pt. No.	Dose (μg/kg)	Reason
009	50	Intracerebral bleed during nadir
010	75	Intolerable grade 2 constitutional and edema
012	75	Central catheter thrombosis
013	100	Right parietal cerebrovascular accident
016	50	Central catheter thrombosis

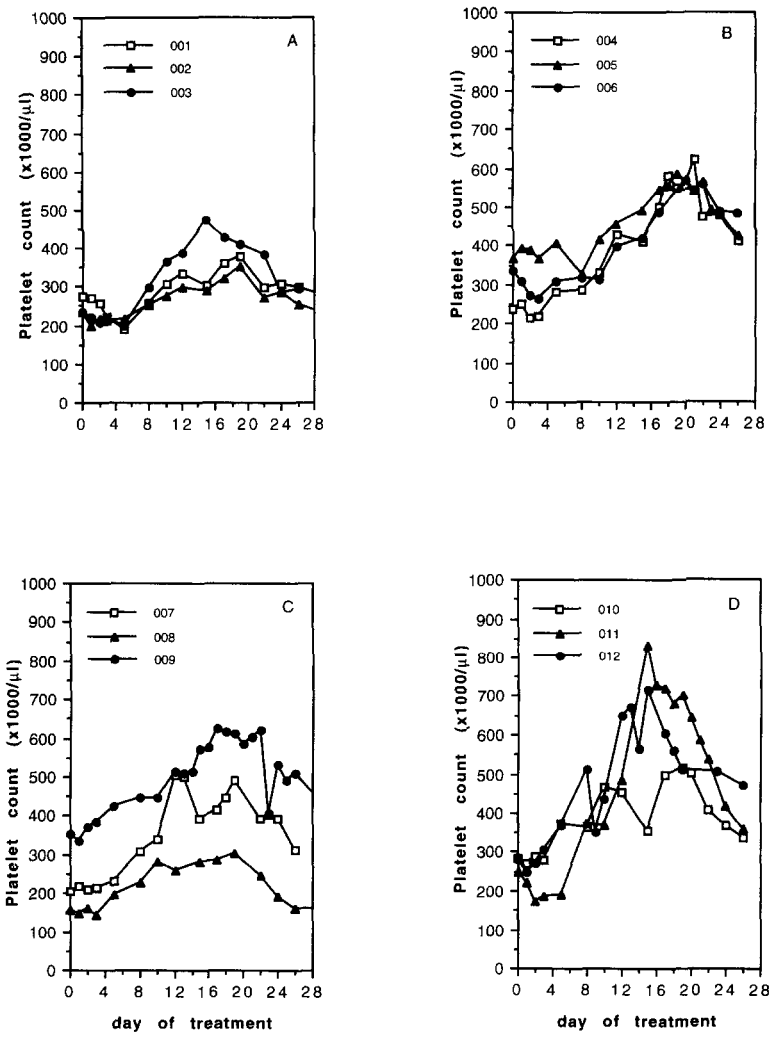

Fig 2. Thrombopoietic effect of rhIL-11 during cycle 0. Before the administration of chemotherapy, rhIL-11 was administered for 14 consecutive days (days 1 through 14) followed by 14 days of observation (days 15 through 28). Platelet counts for all patients treated at the 10-, 25-, 50-, and 75-μg/kg/d dose levels are shown in (A) through (D), respectively.

the four dose levels, respectively. After completion of rhIL-11 therapy, platelet counts gradually decreased, and all returned to baseline pretreatment values by the initiation of cycle 1. There were no significant changes in the mean platelet volume after IL-11 therapy at any doses studied and platelet aggregometry performed pretreatment and on day 15 demonstrated no consistent evidence of an IL-11–related effect on platelet function.

IL-11 was associated with a decrease in hematocrit which, at the doses studied in this trial, was not dose-related. This phenomenon is graphically displayed in Fig 3A and B. An initial decrease in hemoglobin levels was identified within 48 hours of the initiation of therapy and continued through the course of treatment. A mean 20% decrease in hematocrits was identified for all patients at all doses. This effect was associated with a modest reticulocytosis (data not shown). IL-11 had no detectable effects on the numbers of WBCs or subsets of WBCs.

Hematologic effects of IL-11 after chemotherapy. Of the 16 patients enrolled on the study, 12 received rhIL-11 at their assigned dose after at least two cycles of chemotherapy. The median platelet counts for the first cycle of chemotherapy are shown in Fig 4. Although no patient developed severe thrombocytopenia in the first cycle of chemotherapy (defined as a platelet count $<20{,}000/\mu L$), the median nadir platelet counts for patients receiving rhIL-11 at doses ≥ 25 mg/kg/d appear to be higher compared with those patients treated at the 10-μg/kg/d dose. Table 5 reports the nadir platelet counts for each patient across the first two cycles of planned chemotherapy. Mean nadir platelet counts of 67, 159, 152, and $161{,}000/\mu L$ were seen during the first cycle in the 10-, 25-, 50-, and 75-μg/kg/d dose levels, respectively. This apparent attenuation of thrombocytopenia at doses of 25, 50, and 75 μg/kg was also evident during the second cycle of therapy where mean nadir platelet counts of 44,000, 140,000, 126,000, and $102{,}000/\mu L$ were seen for the four doses, respectively. Unfortunately, patient drop-out (only 9 patients completed cycle 3 and 7 completed cycle 4) makes the evaluation of IL-11's effects on thrombocytopenia in the latter two cycles difficult. However, there does appear to be a trend toward a continued attenuation of severe thrombocytopenia at doses ≥ 25 μg/kg/d. Platelet transfusions were

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