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/arthritis 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/arthritis 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 hemocrit 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 studied doses, 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.

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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 IIIIB) 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/m², 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, indication to delaying chemotherapy for 4 weeks, or were receiving treatment with corticosteroids, aspirin, nonsteroidal anti-inflammatory agents, or anticoagulant drugs were excluded. 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 [3H]-thymidine incorporation in a responsive cell line and was >0.6 × 10⁶ 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 commerically.

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/m² and doxorubicin 60 mg/m² 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).
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 cell 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 immunosorbent 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 III B, 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 III B 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...
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).

**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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 platelet counts.
Phase I Trial of rhIL-11

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 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/μL), 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/μL 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/μL 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...
During cycle 0, a transient rhIL-11–related anemia was identified. Hematocrit values for patients treated at the 10- and 25-μg/kg (A) as well as 50- and 75-μg/kg (B) dose levels are shown. The anemia was rapid in onset and maximal on or about day 14 of the cycle. Gradual recovery to pretreatment levels were seen after completion of rhIL-11 therapy. No patient required transfusion for this rhIL-11–related anemia.

required once each during cycles 3 and 4 in only one patient in the 10 μg/kg cohort (patient 001).

IL-11 administration did not appear to increase the degree of chemotherapy-induced anemia. A mean 20% decrease in hematocrits was seen across all cycles of therapy similar to that seen in cycle 0. Similar to the anemia seen in cycle 0, the IL-11–related anemia in the chemotherapy cycles was generally reversible after completion of IL-11 therapy. Although there did appear to be a component of cumulative myelosuppression in those patients receiving three to four cycles of chemotherapy, the impact of the IL-11 in any given cycle appeared to be constant during each of the cycles of therapy. Eight patients were transfused with packed red blood cells a total of 11 times, with three of these eight patients having two transfusions each.

IL-11 did not ameliorate the leukopenia or neutropenia associated with our moderately dose-intensive chemother-

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**Table 5. Effect of rhIL-11 on Platelet Counts After Chemotherapy (Cycles 1 and 2)**

<table>
<thead>
<tr>
<th>Dose (μg/kg)</th>
<th>Pt. No.</th>
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<th>Cycle 2 (x1,000/μL)</th>
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<td></td>
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* Data not available because patient discontinued participation in study.
apy. Based on this observation, patients experiencing severe neutropenia (defined as an absolute neutrophil count <500 cells/µL for >5 days) or an episode of neutropenic fever in cycles 1 or 2 were allowed to receive standard regimens of G-CSF (5 μg/kg SC once daily) in cycles 3 and 4. A total of 33 cycles of chemotherapy were administered without G-CSF, whereas seven patients were treated with G-CSF during a total of nine cycles of chemotherapy. During cycles in which G-CSF was not administered, patients experienced a mean of 6.58 ± 1.5 days of neutropenia (range, 5 to 10 days) compared with a mean of 2.56 ± 1.4 days of neutropenia (range, 0 to 5 days) in cycles during which G-CSF was administered. This result was highly statistically significant (P < .001). This concomitant use of IL-11 and G-CSF was not associated with any additional unexpected adverse events in any of the patients treated.

Effects of IL-11 on blood chemistries. No significant changes in either renal or hepatic function were seen related to IL-11 therapy. A mean 16.25% reduction in total cholesterol levels was seen comparing baseline levels to nadir values, for all dose levels. Cholesterol nadirs occurred on day 3 of dosing in all patients. These reductions in cholesterol appeared to be related to reduction in both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol. Similar changes were not typically seen in serum triglyceride levels. The effect of IL-11 on cholesterol did not appear to be dose-related and was transient. A non–dose-related mean 18.75% reduction in total serum protein and a mean 16.25% reduction in total cholesterol was statistically significant by day 5 through day 15 for all doses compared with baseline pretreatment values (P < .05). A rapid return to pretreatment levels after the completion of rhIL-11 therapy was seen at all doses.

Fig 5: Effect of rhIL-11 on CRP during cycle 0. The administration of rhIL-11 was associated with a dose-related increase in mean CRP levels for patients treated at all doses during cycle 0. This increase was statistically significant by day 5 through day 15 for all doses compared with baseline pretreatment values (P < .05). A rapid return to pretreatment levels after the completion of rhIL-11 therapy was seen at all doses.

DISCUSSION

Thrombocytopenia caused by the administration of dose-intensive chemotherapy has become an increasingly significant problem. The use of G-CSF and GM-CSF to reduce the incidence of febrile neutropenic complications has allowed further dose escalation beyond previous hematologic limitations.12 As a result, patients are frequently exposed to doses of chemotherapy that are associated with greater degrees of myelosuppression, especially thrombocytopenia. In addition, the development of cumulative hematologic toxicity resulting in significant degrees of anemia and thrombocytopenia have redefined the ability to deliver planned doses of chemotherapy on schedule. Recent data support the use of erythropoietin to reduce the cumulative toxicity of chemotherapy on erythropoiesis.14 Unfortunately, no hematopoietic growth factor to date has demonstrated the ability to reduce the degree of chemotherapy-induced thrombocytopenia. At the present time, clinicians are limited to the use of platelet transfusions and/or dose reductions to support such patients. Although effective therapy, platelet transfusions are inconvenient, potentially toxic, and associated with the risk of the development of alloimmunization.15

We performed a phase I trial of rhIL-11, a new hematopoietic growth factor with preclinical thrombopoietic activity, to evaluate its safety as well as its ability to reduce the
Development of thrombocytopenia in women with breast cancer receiving dose-intensive chemotherapy. Although the maximally tolerated dose was not formally identified (based on the protocol definition of two or more dose-limiting toxicities at a dose level), dose escalation of rhIL-11 was discontinued following the development of the cerebrovascular event in the first patient treated at a dose of 100 μg/kg/d. This decision was based on the observation that the intensity of the constitutional symptoms observed in patients treated at doses <100 μg/kg appeared to be increasing in a dose-related manner. While the WHO common toxicity criteria does not quantify constitutional symptoms, subjective interpretation of patient complaints supported this conclusion. At the 75-μg/kg dose level, patients found that their constitutional complaints were significant enough so as to limit their ability to carry out their normal daily routines. This was particularly true of the diffuse myalgias and arthralgias that accompanied therapy at this dose level. Based on the decision to halt dose escalation, not formally defined by the criteria established at the beginning of the study, 75 μg/kg/d would be identified as the maximally tolerated dose in this phase I trial. However, because of the subjective degree of constitutional complaints by patients at this dose, expansion of the 50-μg/kg dose level was undertaken with an additional three patients to further identify the safety of this better tolerated dose level.

The cerebrovascular accident in the patient treated at the 100 μg/kg dose was not associated with an IL-11–induced thrombocytosis nor changes in her infection. Among the remaining 14 patients, only 2, also treated at the 50-μg/kg dose level, experienced thrombosis of indwelling central venous access devices. This common complication may be more related to technical aspects of catheter placement in patients with malignancies, a known risk factor for thrombosis. Among the remaining patients no clinical evidence of thrombosis was seen. As noted previously, platelet aggregometry studies were performed at baseline and after 14 days of rhIL-11 therapy in all patients and demonstrated no consistent change in platelet function. Although fibrinogen levels increased in patients treated at all doses, only at the 75-μg/kg dose level was a sustained statistically significant increase noted. Evaluations of standard coagulation profiles including PTs and PTTs similarly showed no evidence consistent with coagulation activation. Additional studies with rhIL-11 in normal volunteers has demonstrated findings similar to those noted above. In addition, increases in plasma levels of von Willebrand factor have been seen.60 These changes in coagulation factors are rapidly reversible on discontinuation of IL-11 and, could potentially be of benefit to patients who are severely thrombocytopenic with regard to preventing serious bleeding complications.

Other than the patient treated at the 100-μg/kg dose level noted above, no patient experienced grade 3 or greater dose-limiting toxicity related to rhIL-11 administration. The principal adverse events associated with rhIL-11 were constitutional symptoms (arthralgias and myalgias), fatigue, and a dependent extremity edema. These effects developed principally in the latter half of the 14 days of rhIL-11 dosing and reversed after the completion of therapy. While at no time dose-limiting, the constitutional side effects were of a greater intensity at doses of 50 μg/kg and higher as indicated by the greater percentage of patients with WHO grade 2 adverse events. Patients at the 10- and 25-μg/kg doses tolerated therapy exceptionally well with few clinically significant side effects related to rhIL-11. An important observation is that rhIL-11, unlike other hematopoietic growth factors (such as GM-CSF, IL-3, or IL-6), is not associated with fever. This is particularly interesting given the fact that although other agents in the same family as IL-11 (such as IL-6, leukemia inhibitory factor, and ciliary neurotrophic factor) have individual cell surface receptors, their postreceptor signaling pathway, mediated via GP-130, is the same. This suggests that receptor numbers or location may play a role in some of the differences in activity as well as adverse events associated with these agents. Neither capillary leak syndrome nor renal or hepatic dysfunction were identified in any of the patients treated.

Antibody formation was confirmed for one patient. A second patient demonstrated an antibody response that was consistent with antibody formation as a result of product exposure but had insufficient sample to confirm specificity to the rhIL-11 protein. In both cases, the antibody titers were below the level which has previously been characterized as having neutralizing capacity, and hence were not felt to be of clinical significance.

Treatment with rhIL-11 is associated with a therapy-related anemia that is rapid in onset, reversible, and not associated with any evidence of hemolysis or occult blood loss. Although patients in this study were phlebotomized frequently for laboratory studies, this volume was insufficient to account for the degree of anemia seen. Further investigations identified the fact that patients receiving rhIL-11 develop a significant expansion of their plasma volume which contributes to the development of a dilutional anemia. Although this may not be the only mechanism involved, it appears from our studies to be the predominant one. Other investigators have reported similar findings regarding the anemia related to IL-11 and IL-6 and have reached a similar conclusion, validating our findings.17-19

The hematologic effects of rhIL-11 were assessed independently during the 28-day prechemotherapy safety period termed cycle 0. During this time patients received rhIL-11 at their assigned dose for 14 days followed by 14 days of observation. The administration of rhIL-11 was associated with an initial decrease in platelet counts followed by a dose-related increase in platelets with peak platelet counts occurring after the completion of rhIL-11 therapy. A gradual return to pretreatment platelet counts occurred over the ensuing 2 weeks of observation. The initial decrease in platelet count is possibly the result of an early rapid increase in
plasma volume but its pathogenesis remains unknown. Laboratory studies performed in conjunction with this trial have demonstrated that rhIL-11 exerts a maturational effects on BM megakaryocytes (MKs) resulting in increased BM MK ploidy. In preclinical models, these ploidy changes have been directly associated with the thrombopoietic effects of rhIL-11 as well as other similar agents. No effects on WBCs or WBC subsets related to IL-11 therapy were seen. This is in contrast to some of the preclinical murine data, but is similar to the data generated in normal nonhuman primates.

After the administration of the first cycle of chemotherapy, patients receiving rhIL-11 at the 10-µg/kg dose developed moderate thrombocytopenia that appeared to worsen in cycle 2. In comparison, patients treated at doses of 25 µg/kg and higher experienced less thrombocytopenia after the administration of cycles 1 and 2 of chemotherapy. In our prior experience with this chemotherapy regimen in patients treated without CSFs the degree of thrombocytopenia was similar to that seen in the 10-µg/kg cohort, suggesting that the attenuation of thrombocytopenia at doses ≥25 µg/kg is directly related to the administration of rhIL-11. Unfortunately, patient drop-out at the two higher doses precluded the treatment of a sufficient number of patients in the latter two chemotherapy cycles to substantiate rhIL-11’s ability to attenuate the development of cumulative thrombocytopenia. This benefit does appear to be evident in patients receiving the 25 µg/kg dose where two of the three patients completed all four cycles of chemotherapy. Neither of these patients developed significant thrombocytopenia compared with the patients at the 10-µg/kg dose, one of whom required platelet transfusions for severe thrombocytopenia in cycles 3 and 4. Because the primary objective of this study was rhIL-11’s safety and not its ability to abrogate chemotherapy-induced thrombocytopenia, we did not treat sufficient numbers of patients to allow statistical analysis of rhIL-11’s thrombopoietic effect. In addition, our chemotherapy regimen, although moderately intensive, does not characteristically induce severe thrombocytopenia. Hence, while we can identify what appears to be a potentially beneficial effect of rhIL-11 at doses ≥25 µg/kg/d, future phase II trials with this agent will need to focus on its ability to reduce thrombocytopenia with more myelosuppressive regimens.

After the recognition that rhIL-11 does not exert a stimulatory effect on myeloid cells, the protocol was amended to allow the administration of G-CSF during cycles 3 and 4 in patients who experienced morbidity related to severe neutropenia during cycles 1 or 2. We were able to safely combine G-CSF with rhIL-11 without the identification of any new or more severe adverse events. In these patients, rhIL-11 continued to exert its anticipated thrombopoietic effects while G-CSF exerted its expected myeloid effect. Although each cycle of therapy was associated with the expected transient rhIL-11–related anemia, this did not appear to worsen the cumulative anemia often seen with chemotherapy.

Preclinical models have shown that the administration of IL-11 is associated with an increase in a variety of acute-phase proteins. We observed an apparent dose-related increase in CRP for doses ≥25 µg/kg in all cycles of therapy. In addition, a non–dose-related increase in fibrinogen levels that was statistically significant at the two highest doses was identified. This increase may be of particular value in patients suffering from severe thrombocytopenia with regard to potentially decreasing their risk of hemorrhagic complications. Reductions in total serum cholesterol, total protein, and albumin were seen and appear to be related to the expansion of the plasma volume.

In conclusion, we have shown that rhIL-11 can be safely administered at doses ranging from 10 to 75 µg/kg/d for up to 14 days. Side effects are primarily constitutional in nature but, importantly, do not include fever. These adverse events appear to be dose-related, with relatively few clinically significant complaints at doses ≥50 µg/kg/d. Prechemotherapy administration of IL-11 is associated with a dose-related thrombopoietic effect, although no effects on the myeloid or erythroid lineages are seen. All patients experienced anemia due primarily to plasma volume expansion, as well as an increase in acute-phase proteins that can serve as a biomarker of IL-11 activity. After the administration of chemotherapy in this study, rhIL-11 at doses of ≥25 µg/kg/d appeared to reduce the degree of thrombocytopenia over the course of at least two cycles of dose-intensive chemotherapy compared with patients treated at the lowest dose level. These results suggest that rhIL-11 holds significant promise as a thrombopoietic agent and that doses of 25 or 50 µg/kg/d are well tolerated and potentially effective. Future studies designed to test the ability of IL-11 to abrogate severe thrombocytopenia in patients receiving dose-intensive chemotherapy are underway. In addition, the potential role of IL-11 in the BM transplant and BM failure settings are being explored.

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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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