Clinical Efficacy of rhIL-11

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Placebo-controlled clinical trials of recombinant human interleukin-11 (rhIL-11, also known as oprelvekin [Neumega]) in patients with nonmyeloid malignancies have demonstrated significant efficacy in preventing postchemotherapy thrombocytopenia.

Introduction

Recombinant human interleukin-11 (rhIL-11, also known as oprelvekin [Neumega]), is the only platelet growth factor currently available in the United States for the prevention of chemotherapy-associated severe thrombocytopenia in patients with nonmyeloid malignancies who are at high risk for the development of this condition. The recommended treatment regimen in adults is 50 µg/kg administered subcutaneously, once daily, beginning 6 to 24 hours after completion of the chemotherapy cycle and continuing until the platelet count is ≥ 50,000/µL. Individual treatment courses longer than 21 days are not recommended, and the drug should be discontinued at least 2 days before the start of the next chemotherapy cycle.

The results of several clinical trials have established the role of rhIL-11 as a thrombopoietic growth factor. Dose-ranging[1] and placebo-controlled[2,3] clinical trials of rhIL-11 in adults and open clinical trials of rhIL-11 in children[4,5] undergoing chemotherapy for solid tumors or lymphoma have provided clinical evidence of attenuation of platelet nadir and stimulation of platelet production. These trials have shown that rhIL-11 accelerates the recovery of platelet counts, facilitating the administration of the planned chemotherapy without dose modification. This article presents background pharmacologic information and a discussion of data from clinical trials supporting the efficacy of rhIL-11, through its thrombopoietic effects, for the prevention of chemotherapy-induced severe thrombocytopenia in high-risk patients with nonmyeloid malignancies.

Pharmacologic Properties

rhIL-11 is well absorbed subcutaneously with a bioavailability of more than 80%; repeated doses do not accumulate in plasma.[6] The pharmacodynamic properties of rhIL-11 were determined in a phase I dose-ranging study in nonmyelosuppressed patients (age range: 26 to 67 years) with locally advanced (stage IIIB, n = 3) or metastatic (stage IV, n = 13) breast cancer.[1] rhIL-11 was administered both before (cycle 0) and after up to four monthly cycles of dose-intensive chemotherapy.

After a 14-day washout period following the prechemotherapy dosing of rhIL-11, patients received two to four cycles of chemotherapy with cyclophosphamide (Cytoxan, Neosar) at a dose of 1,500 mg/m² and doxorubicin at 60 mg/m² administered on the first day of each cycle. Chemotherapy was repeated every 28 days. Cohorts of at least three patients received rhIL-11 alone at doses of 10, 25, 50, 75, or 100 µg/kg/d subcutaneously for 12 days (days 3 through 14 of each treatment cycle). The use of granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) (5 µg/kg/d) was permitted during the third and fourth chemotherapy cycles if patients experienced a febrile neutropenic event or an absolute neutrophil count (ANC) of ≤ 500/µL for more than 5 days during the first two cycles.

Effects of rhIL-11

Thrombopoietic Effects

In nonmyelosuppressed patients (ie, cycle 0, prior to chemotherapy), daily dosing with rhIL-11 over the dose range of 10 to 75 µg/kg produced a dose-dependent rise in platelet count that was apparent between 5 and 9 days after the start of dosing (Figure 1). Platelet counts reached peak levels after a median of 14 to 19 days. Figure 1 shows the platelet-response profile at doses of 10, 25, and 50 mg/kg per day.[1,7] These doses produced increases in platelet counts of 76%, 93%, and...
108%, respectively, from baseline values. At the 50-µg/kg/d dose, peak platelet counts occurred at a median of 16 days after the initiation of therapy. As seen in Figure 1, increases in platelet counts were sustained for approximately 1 week after rhIL-11 was discontinued. At the 75-µg/kg/d dose, an increase of 185% over the baseline value was observed.

Across two chemotherapy cycles (myelosuppressed state), rhIL-11 doses ≥ 25 µg/kg/d produced higher median nadir platelet counts (> 100,000/µL) than the 10-mg/kg/d dose (< 70,000/µL). Only doses that were ≥ 25 µg/kg/d prevented severe thrombocytopenia (defined as a platelet count < 20,000/µL, the level often used as a threshold for platelet transfusion).

**Effects on Platelet Function and Coagulation Factors**

Treatment with rhIL-11 had no apparent effect on platelet function. There were no changes in either adenosine diphosphate (ADP)-induced platelet activation or platelet aggregation induced by various agents (ADP, epinephrine, collagen, ristocetin, or arachidonic acid), indicating a lack of effect of rhIL-11 on platelet reactivity or platelet aggregating behavior, respectively. At all doses studied, treatment with rhIL-11 was not associated with significant changes in prothrombin time or partial thromboplastin time.

At the 50-µg/kg/d dose, a statistically significant increase from baseline in mean fibrinogen level was seen by day 12 of treatment. These findings are in accordance with those of an earlier study in healthy adult volunteers in which treatment with rhIL-11 (25 µg/kg/d subcutaneously for 7 days), resulted in statistically significant increases in mean plasma fibrinogen concentration and mean von Willebrand factor, compared with both baseline and placebo (fibrinogen: P < .001 vs baseline, P < .01 vs placebo; von Willebrand: P < .001 vs baseline, P = .02 vs placebo).[8]

**Other Effects**

In this study, rhIL-11 alone (without G-CSF) did not ameliorate chemotherapy-associated leukopenia or neutropenia, suggesting that the predominant biological activity of rhIL-11 is on the megakaryocytic cell lineage, contrasting with the stimulation of other hematopoietic lineages observed in vitro.[9] There was no evidence of interference by rhIL-11 on the efficacy of G-CSF in ameliorating neutropenia when these cytokines were administered concurrently. This is an important finding because the simultaneous use of these two cytokines addresses the two major dose-limiting toxicities of myelotoxic chemotherapy.

Treatment with rhIL-11 was associated with dose-related increases in acute-phase proteins during both pre- and postchemotherapy cycles. At all doses studied, maximal increases in C-reactive protein occurred within the first week of therapy and remained at statistically significantly (P < .05) elevated levels from day 5 through day 15, compared with baseline pretreatment levels. Levels of C-reactive protein rapidly returned to baseline levels following discontinuation of rhIL-11.

Treatment with rhIL-11 was associated with an expansion in plasma volume of approximately 20%, which is believed to occur secondary to rhIL-11 stimulation of renal sodium reabsorption.[10] The reversible expansion in plasma volume led to the development of dependent peripheral edema and dilutional anemia as two of the most commonly reported side effects. Edema and constitutional symptoms (myalgia, arthralgia, headache, and fatigue) were primarily considered to be mild or moderate in severity at rhIL-11 doses of ≤ 50 µg/kg/d.

Edema was also a common occurrence during subsequent controlled clinical evaluations of rhIL-11 at 50 µg/kg, but it was usually mild to moderate, easily managed, and either resolved spontaneously or relieved by temporary use of a diuretic.[2,3] In these studies, plasma volume expansion was also the most likely underlying cause of other observed side effects, such as palpitations, dyspnea, headache, and transient atrial arrhythmias. Increased plasma volume may have contributed to the development of atrial arrhythmias in a subset of patients by causing atrial distention (which has been demonstrated in dogs treated with rhIL-11[11]) and a subsequent decrease in the atrial refractory period.[12]

In patients with cancer, transtelephonic monitor data showed no evidence of any effects of rhIL-11 treatment on cardiac conduction intervals, specifically PR, QRS, QT, or QTc intervals, indicating that rhIL-11 has no direct effect on cardiac function.[6]

rhIL-11 did not cause clinically significant fevers or capillary leak syndrome. The 75-µg/kg/d dose was not associated with true dose-limiting toxicity but was subjectively less well tolerated than lower doses. Thus, evaluation of this dose was not pursued in subsequent studies.

**Randomized Clinical Studies of rhIL-11**

Three randomized, double-blind, placebo-controlled studies (studies I and II and a phase III study) have demonstrated the efficacy of once-daily rhIL-11 treatment at a dose of 50 µg/kg.
subcutaneously in ameliorating chemotherapy-induced thrombocytopenia.[2,3,13] In all three studies, patients received chemotherapy followed by rhIL-11 or placebo. Full doses of chemotherapy were administered; no dose reductions for thrombocytopenia were allowed. Treatment with placebo or rhIL-11 was begun 1 day after the completion of chemotherapy and continued for a total duration of 14 to 21 days. None of the patients in the study received hematopoietic stem-cell support. The randomized phase II studies I and II were similar in design, whereas the protocol for the phase III study differed slightly from these two studies. Therefore, the design elements and results of the phase III study are discussed separately. Both published and unpublished results of the three studies are presented here.

**Design Elements of Studies I and II**

The main design elements of the randomized phase II studies I and II are summarized in Table 1. In both studies, chemotherapy-induced thrombocytopenia (CIT) was defined as chemotherapy-induced lowering of platelet counts to levels of \(\leq 20,000/\mu\text{L}\) in a previous cycle of chemotherapy. These studies administered rhIL-11 as \(\text{secondary prevention.}\) meaning the prevention of severe CIT following a documented episode of CIT in the prior chemotherapy cycle. The development of CIT commonly triggers the administration of prophylactic platelet transfusions and chemotherapy dose reduction in subsequent cycles. Platelet counts of \(\leq 20,000/\mu\text{L}\) were chosen as the platelet level defining CIT, although the definition of CIT is known to vary. Platelet counts were monitored three times weekly and repeated daily if the most recent count was \(\leq 50,000/\mu\text{L}\). Platelet transfusions were administered if the platelet count was \(\leq 20,000/\mu\text{L}\) or if clinically indicated to reduce the risk of bleeding.

The primary efficacy end point in both studies I and II was the proportion of patients who did not require platelet transfusions over one cycle (study I) or two cycles (study II) of chemotherapy. Avoidance of platelet transfusion (defined as \(\text{response}\) in these studies) can therefore be viewed as an objective surrogate measure of the ability of rhIL-11 to prevent the reduction of platelets to nadirs of \(\leq 20,000/\mu\text{L}\).

Secondary end points in both studies were the number of platelet transfusions per patient; the time to recovery to platelet counts of 20,000/µL, 50,000/µL, and 100,000/µL; and the duration of platelet nadirs below these thresholds. These end points are meaningful because shortening the recovery time from low platelet counts lowers the duration of exposure to associated risks. For example, the number of platelet transfusions correlates with an aggregate risk of a transfusion-related complication. The recovery period to a platelet count of 20,000/µL represents the period of greatest risk of bleeding and the time during which patients most often receive prophylactic platelet transfusions.

The recovery period to a platelet count of 50,000/µL correlates with the time during which patients are closely monitored for the development of more severe CIT and during which special precautions are often taken to avoid injury that could result in bleeding. Recovery to a platelet count of 100,000/µL is the threshold at which it is generally considered appropriate to administer the next cycle of chemotherapy.[14] Below this threshold, the next cycle is often delayed and/or given at reduced doses. [3,14-17]

Furthermore, with successive chemotherapy cycles, lower platelet nadirs are expected to occur due to cumulative thrombocytopenia. Thus, when started at 6 to 24 hours following the last dose of chemotherapy, the ability of rhIL-11 to accelerate recovery to platelet counts of \(\geq 50,000/\mu\text{L}\) or 100,000/µL supports the continuation of chemotherapy at full doses and without dose delay. Furthermore, the suggested association of delivery of optimal doses with improved rates of disease remission and overall survival[18-24] makes shortening the time of platelet recovery to established thresholds an important clinical end point.

**Study I**

Study I [2,6] was designed to assess the ability of rhIL-11 doses of 25 \(\mu\text{g/kg/d (n = 31)}\), 50 \(\mu\text{g/kg/d (n = 32)}\), or placebo (n = 30), administered once daily for 14 to 21 days, to prevent the recurrence of thrombocytopenia during a subsequent chemotherapy cycle. Chemotherapy-induced thrombocytopenia was predicted to occur at a rate of virtually 100% in untreated patients during the study cycle, because only patients who experienced CIT severe enough to warrant platelet transfusion (platelet count nadir < 20,000/µL) during the most recent prior cycle of chemotherapy were admitted to the study. Because CIT tends to increase in severity during subsequent cycles of a particular regimen unless doses of chemotherapy are reduced, the study protocol requirement for continuation of the same chemotherapy regimen without dose reduction allowed rigorous testing of the efficacy of rhIL-11.

At baseline, all of the study patients had recovered from myelosuppression caused by previous...
chemotherapy as judged by platelet counts \(\geq 100,000/\mu L\), ANC \(\geq 1,000/\mu L\), and hemoglobin \(\geq 9.5\) g/dL. Overall, patients were treated with 24 different chemotherapeutic regimens for a variety of cancers, including breast cancer (n = 23), non-Hodgkin’s lymphoma (n = 19), non-small-cell lung cancer (n = 7), Hodgkin’s disease (n = 6), and ovarian cancer (n = 5). The most commonly used regimens were DICEP (dose-intensive cyclophosphamide/etoposide/cisplatin [Platinol]; n = 19) and ICE (ifosfamide [Ifex]/carboplatin [Paraplatin]/etoposide; n = 13). All but three patients received concomitant G-CSF therapy.

**Study II**
In contrast to the population in study I, the population in study II[3,6] was homogeneous with respect to cancer type (breast cancer) and gender (100% women). G-CSF was also coadministered following chemotherapy. Study patients had no history of CIT but were expected to be at high risk because the high-dose cyclophosphamide/doxorubicin regimen used in this study produced severe thrombocytopenia in a previous trial.[25] Most patients in this trial had not received prior chemotherapy (rhIL-11 group, 68%; placebo group, 73%). There were 40 patients in the rhIL-11 50-µg/kg treatment group and 37 in the placebo group. After 10 days of treatment, rhIL-11 was discontinued if the platelet count was \(\geq 50,000/\mu L\) without a platelet transfusion in the previous 2 days, or continued for another 7 days if the platelet count was \(\leq 50,000/\mu L\) or a transfusion was needed within the past 2 days. Due to the effects of rhIL-11 on fluid retention and hemodilution observed in study I, a diuretic (hydrochlorothiazide 50 mg, triamterene [Dyrenium] 75 mg) was recommended if a patient’s hemoglobin concentration was less than 9 g/dL. Furosemide was administered if urine output was inadequate.

**Primary Efficacy End-Point Analysis of Each Study**
For each study, primary efficacy end-point analysis was performed in the intent-to-treat group (all randomized patients), the evaluable subgroup (patients for whom the primary efficacy outcome could be determined with a high degree of certainty), and the completers subgroup (all patients who received the prescribed amount of treatment in the required number of cycles with no major protocol violations).

In study I, the rhIL-11 treatment dose of 25 mg/kg was found to be ineffective. Although 6 of 30 (20%) patients in the intent-to-treat group and 5 of 28 (18%) evaluable patients who were treated at this dose level avoided platelet transfusions, this response rate did not differ significantly from that seen with placebo (6% and 4%, respectively; \(P > .23\)).[2]

In both studies, the intent-to-treat analysis showed that a significantly \((P \leq .02)\) higher proportion of patients treated with rhIL-11 50 µg/kg/d did not require platelet transfusions compared with placebo (Table 2). In the evaluable subgroup analysis, a significantly \((P < .02)\) higher proportion of patients treated with rhIL-11 avoided platelet transfusions in study I and a trend \((P = .08)\) toward a similar successful outcome was seen in the evaluable subgroup analysis in study II.

Also in both studies, a significantly \((P \leq .02)\) higher proportion of rhIL-11–treated patients in the completers subgroup avoided platelet transfusions compared with placebo.

These data indicate that treatment with rhIL-11 50 µg/kg/d significantly reduces the incidence of thrombocytopenia to levels meeting the study protocol definition of CIT \((\leq 20,000/\mu L)\), as judged by the significantly higher proportion of patients who avoided platelet transfusions. The data from study I also indicate that the 25-µg/kg dose of rhIL-11 is not effective and should not be used in clinical practice. The data suggest that 50 µg/kg/d is an effective dose for the prevention of chemotherapy-induced reduction of platelets to \(\leq 20,000/\mu L\) in adult patients with solid tumors and lymphomas, and support the continuation of planned doses, on timely schedules.

**Combined Analyses of Studies I and II**
A combined analysis (Table 3) of data from the intent-to-treat populations in these two studies \((n = 139)\) showed that treatment with rhIL-11 50 mg/kg significantly reduced the risk of receiving any platelet transfusions during the applicable study cycle(s) by 40% (95% confidence interval: 0.5 to 0.8) relative to placebo \((P < .001)\).

The results from the combined analysis reflected findings in the individual studies. For example, in study I, the median number of transfusions required by patients in the 50-µg/kg, 25-µg/kg, and placebo evaluable subgroups were 1, 2, and 3, respectively. The reduction in the median number of transfusions for the rhIL-11 50-µg/kg group approached statistical significance compared with the placebo group \((P = .06)\).[2]

In study II, the evaluable subgroup analysis found that patients who received rhIL-11 50 µg/kg required a significantly \((P = .04)\) lower mean number of transfusions \((0.8; \text{range: } 0[6])\) compared with placebo recipients \((2.2; \text{range: } 0[18])\).[3] There was also a statistically significant \((P = .04)\) difference in the median number of transfusions required by rhIL-11 recipients \((0)\) and by placebo recipients.
Effects on Platelet Recovery Time

Treatment with rhIL-11 50 µg/kg/d tended to shorten the time to recovery to platelet counts of 20,000/µL, 50,000/µL, and 100,000/µL compared with placebo in patients receiving highly myelotoxic regimens. The difference between rhIL-11 and placebo in median time to recovery to 20,000/µL was statistically significant (0 days vs 11 days, respectively; P = .03). Although the combined analysis did not show a significant difference between rhIL-11 and placebo for recovery to 50,000/µL, the separate evaluable subgroup analysis for study II showed a significantly (P = .01) shorter mean time to recovery to platelet count ≥ 50,000/µL among patients treated with rhIL-11 50 µg/kg (9.3 days) compared with placebo-treated patients (13 days) during the second cycle of chemotherapy.[3] In this study, all patients at risk for the development of CIT who received rhIL-11 50 µg/kg experienced platelet recovery to ≥ 50,000/µL within 19 days after the start of dosing. Similarly, the duration of platelet counts below these thresholds was generally shorter among rhIL-11–treated patients than among placebo-treated patients. The difference reached statistical significance (P = .03) for the duration of platelet counts < 20,000/µL and approached statistical significance (P = .08) for the duration of platelet counts < 50,000/µL. The blunting of platelet nadirs ≤ 20,000/µL (represented by avoidance of platelet transfusions) and acceleration of platelet recovery was reflected by a substantially lower incidence of bleeding events (including ecchymosis, epistaxis, and hematuria) in the combined rhIL-11 50-µg/kg group (27.5%) compared with the placebo group (50.8%).[6] Severe bleeding events (3) with a severity rating of grade 3 or higher occurred only in the placebo group.

In both studies I and II, patients who avoided platelet transfusions experienced earlier recovery to a platelet count of 100,000/µL than those who received transfusions, as might be expected.[6] An analysis of data pooled from the three double-blind study cycles in these two studies showed a significant (P < .01) association between avoiding platelet transfusions (ie, avoiding platelet nadirs ≤ 20,000/µL) and shorter time to recovery to platelet count of 100,000/µL (Figure 2).[6] Regardless of treatment, by day 21 almost twice as many patients who avoided transfusions (98%) had platelet counts ≥ 100,000/µL, compared with those who required transfusions (56%). Even by day 28, only 78% of patients who required transfusions had platelet recovery to ≥ 100,000/µL. These data imply that prevention of platelet reduction to nadirs ≤ 20,000/µL by treatment with rhIL-11 supports earlier recovery of platelets to thresholds for administering the next cycle of chemotherapy without delay or dose reduction. Thus, the demonstration of earlier platelet recovery with rhIL-11 treatment to platelet counts of 50,000/µL and 100,000/µL implies that rhIL-11–treated patients would be more likely to receive their next chemotherapy cycle at full doses and at the scheduled time, or at least sooner than patients not receiving rhIL-11. Several retrospective and some prospective analyses suggest that full-dose, on-time management may improve long-term outcomes.[18-24]

Multiple Chemotherapy Cycles

The sustained efficacy of rhIL-11 over multiple chemotherapy cycles is supported by data from the optional open-label cycles (one cycle in study I and up to four cycles in study II) that followed the double-blind study cycles. Patients were allowed treatment with rhIL-11 during these cycles, provided they continued to receive the same chemotherapy regimen with no dose reductions. In study II, platelet transfusion was avoided in 53% of 36 patients (17 from the rhIL-11 group and 19 from the original placebo group) treated with rhIL-11 in the third cycle and 59% of 17 patients (8 from the rhIL-11 group and 9 from the original placebo group) treated in the fourth cycle.[3] Combined analysis from all chemotherapy cycles (blinded and open-label) in studies I and II showed that among patients treated with rhIL-11 50 mg/kg/d, 69% (34/49) avoided platelet transfusions over two or more open-label cycles: 59% (10/17) over three or more cycles, and 50% (4/8) over four or more cycles.[6]

No Adverse Pharmacodynamic Interaction With G-CSF

In both controlled studies, concurrent rhIL-11 therapy had no effect on the efficacy of G-CSF, confirming the findings in the dose-ranging study.[1] This was evidenced by the absence of between-group differences in the incidence or severity of neutropenic fever in study I. Also, in study II, the mean times to neutrophil recovery after cycles 1 and 2 were similar among rhIL-11–treated patients (7.8 and 7.6 days, respectively) and placebo-treated patients (10.5 and 7.9 days). However, in subsequent clinical trials (discussed below),[4,5,13] an increased effect with the combination of rhIL-11 and G-CSF on myeloid recovery following chemotherapy was observed.

Phase III Study

The results of a multicenter, randomized, double-blind, placebo-controlled phase III study[6,13] (n =
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133) confirmed and expanded the findings from studies I and II. In this trial, patients with solid tumors or lymphoma receiving various chemotherapy regimens and who had platelet nadirs < 25,000/µL during the cycle prior to study entry were randomized to 14 days of treatment with either daily rhIL-11 50 µg/kg subcutaneously (n = 88) or placebo (n = 45), each started after chemotherapy was completed (identical agents, doses, routes of administration, and schedule as during the previous cycle).

The objective of the phase III study was to compare the proportion of rhIL-11–treated patients vs placebo-treated patients who had a platelet nadir > 20,000/µL and who did not receive any platelet transfusions. The study patients generally had advanced malignancies—most commonly non-Hodgkin’s lymphoma and breast cancer. The three most frequently used chemotherapeutic agents were cisplatin, etoposide, and carboplatin, as components of a variety of chemotherapy regimens. Sixty-seven (76%) patients in the rhIL-11 group and 39 (87%) in the placebo group received G-CSF concomitantly.

During rhIL-11 treatment a complete blood count (CBC), including platelet count, was performed three times weekly until the platelet count reached ≥ 100,000/µL and the ANC increased to ≥ 1,000/µL, after their respective nadirs. The CBC was repeated daily if the most recent platelet count was ≤ 30,000/µL or if the patient had a platelet transfusion the previous day. The primary efficacy end point was the proportion of patients who avoided platelet transfusions and who had a platelet nadir > 20,000/µL during the study cycle. The proportion of patients who avoided platelet transfusions at a platelet nadir > 10,000/µL was included as a secondary efficacy end point because of data supporting the withholding of platelet transfusions until the platelet count decreased to < 10,000/µL.

The intent-to-treat analysis showed that significantly more patients treated with rhIL-11 avoided platelet transfusions at platelet nadirs > 20,000/µL (35% vs 18% with placebo; P = .04) and > 10,000/µL (45% vs 20% with placebo; P = .004). Patients in the rhIL-11 group required significantly fewer platelet transfusions (mean: 1.6 vs 2.2 for placebo; P = .01) and had a higher mean platelet nadir (25,600 vs 19,100/µL with placebo; P = .01). Consistent with the results in study II, treatment with rhIL-11 (n = 127 evaluable patients) tended to shorten the median time to recovery to platelet counts ≥ 20,000/µL (12 vs 14 days with placebo; P = .11), and counts ≥ 50,000/µL (18 vs 21 days with placebo; P = .31).

The median duration of neutropenia (ANC < 500/µL) was significantly shorter in rhIL-11–treated patients than in placebo-treated patients (1 vs 3 days; P = .02), as was the time to recovery to ANC ≥ 500/µL (9 vs 13 days; P = .008). Fewer patients in the rhIL-11 group had an ANC < 500/µL, regardless of G-CSF use. Also, fewer rhIL-11–treated patients tended to experience neutropenic fever than those treated with placebo (12 [14%] vs 13 [29%]; P = .06). In this study, the observation of accelerated neutrophil recovery during treatment with the multifunctional cytokine rhIL-11 supports the preclinical observations of a synergistic stimulatory effect of rhIL-11 on myeloid recovery after chemotherapy in the presence of G-CSF.

Pediatric Experience With rhIL-11

Pharmacokinetic studies in infants, children, and adolescents (age range: 8 months to 17 years) receiving ICE chemotherapy have shown that in the pediatric population, a rhIL-11 dose of 75 to 100 µg/kg produces plasma drug concentrations similar to those obtained with a rhIL-11 dose of 50 µg/kg in adults.[6] Preliminary data also suggest that the rate of clearance of rhIL-11 in infants and children (8 months to 11 years) is approximately 1.2- to 1.6-fold higher than the clearance rate in adults and adolescents ages 12 years and older.

A recent study of rhIL-11 in children receiving chemotherapy with ICE for solid tumors showed that the 75-µg/kg dose was well tolerated by this patient population.[27] The authors suggested that the absence of toxicity at this dose was likely attributed to a more rapid drug clearance rate and an observed lack of induction of inflammatory cytokines by rhIL-11. The ICE chemotherapy regimen is highly myelotoxic; grade IV hematopoietic toxicity occurs in the majority (> 90%) of children despite supportive treatment with G-CSF, frequently limiting dose intensity. Consistent with observations of a synergistic hematopoietic effect, two studies in children (< 21 years of age) with recurrent or refractory solid tumors and receiving ICE chemotherapy found that treatment with the combination of rhIL-11 (100 µg/kg/d) and G-CSF (5 µg/kg/d) enhanced myeloid and platelet recovery more effectively than G-CSF alone.[4,5]

Over one cycle, the combined use of rhIL-11 and G-CSF resulted in shorter recovery time to ANC > 1,000/µL (19 vs 21 days) and reduced rate of infection (33% vs 60%) compared with the use of
G-CSF alone.\[5\] As expected, the addition of rhIL-11 to G-CSF treatment resulted in a statistically significant shorter recovery time to platelet count > 100,000/µL (17 days vs 27 days with G-CSF alone; \(P < .05\)) and in the median number of platelet transfusions (1 vs 12 with G-CSF alone).\[4\] Thus, the combination of rhIL-11 and G-CSF provided multilineage hematopoietic support.

**Practical Clinical Considerations**

rhIL-11 is a prophylactic supportive care agent that has been shown to prevent CIT and promote platelet recovery. Therefore, prophylactic therapy with rhIL-11 should be considered in patients who are likely to develop CIT (Table 4) and, as a result of CIT, would receive reduced chemotherapy doses, and/or experience a delay in treatment, or risk the considerable occurrence of adverse events associated with platelet transfusions.\[6\] In these patients, the administration of reduced chemotherapy doses could also potentially lead to suboptimal treatment outcomes.\[18-24\] Clinical trials have established that the optimal adult daily dose of rhIL-11 is 50 µg/kg. Lower doses (eg, 25 µg/kg) have not demonstrated significant efficacy and should not be used. Pediatric patients appear to tolerate and require higher doses of rhIL-11 (100 µg/kg) because of a more rapid drug clearance. Timing of administration is the key to deriving the maximum thrombopoietic benefit from rhIL-11 therapy. rhIL-11 must be administered within 6 to 24 hours after chemotherapy and before thrombocytopenia develops in that cycle.

In contrast to platelet transfusions, rhIL-11 is not a "rescue" agent. Its use as such is inappropriate and would produce disappointing results, because increases in platelet counts do not occur immediately after the initiation of rhIL-11 dosing. The recommendation to begin rhIL-11 treatment within 24 hours after completion of chemotherapy makes an allowance for the slower process of megakaryocyte growth and platelet development, such that the peak platelet production occurs at and across the expected platelet nadir, usually 10 to 14 days after chemotherapy.\[1\] Dosing beyond 21 days is not recommended because treatment for a longer duration has not been evaluated in controlled clinical trials in patients with CIT.

Discontinuation of dosing once postnadir platelet recovery to 50,000/µL has been achieved is recommended because this platelet threshold is considered to be adequate for hemostasis. Continued dosing beyond this level would not be expected to provide additional clinical benefit. rhIL-11 is generally well tolerated and is capable of providing clinically relevant benefits with a low risk of adverse events serious enough to warrant discontinuation of therapy. Fluid retention and resultant atrial arrhythmias are the most commonly encountered expected adverse events. Careful attention to volume status and early intervention with diuretics when clinically appropriate can minimize this toxicity. If diuretic therapy is initiated, fluids and electrolyte status should be carefully monitored. rhIL-11 should be used cautiously, if at all, in patients with a previous history of congestive heart failure, volume overload, or arrhythmia.

**Conclusions**

Used appropriately, rhIL-11 can significantly ameliorate the severity and duration of thrombocytopenia in patients receiving myelosuppressive chemotherapy. In these patients, rhIL-11 improves the platelet nadir and facilitates platelet recovery to thresholds that permit the continuation of chemotherapy at full doses without delay. Both retrospective analyses and prospective trials\[18-24\] have demonstrated that achieving optimal dose intensity of chemotherapy improves outcomes in a variety of malignancies. By facilitating the delivery of chemotherapy, outcomes may be optimized.

**References:**


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