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ORIGINAL ARTICLE

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Thrombopoietic activity of recombinant human interleukin 11 in cancer patients receiving chemotherapy

Abstract Interleukin 11 (IL-11) is a newly identified hematopoietic growth factor that exerts its primary effect on megakaryocyte maturation and platelet production. It has a unique receptor, signaling by which is mediated by the glycoprotein (GP) 130 pathway. IL-11 is synergistic with stem-cell factor (c-kit ligand) in vitro, enhancing proliferation of primitive hematopoietic stem cells, and has been shown to be critical to the process of polyploidization and maturation. In preclinical models, IL-11 was shown to enhance platelet recovery following intensive chemotherapy, and in murine bone-marrow transplant models it accelerates the recovery of all hematopoietic lineages. Nonhuman primate studies have demonstrated a dose-related thrombopoietic effect; however, no myeloid effect has been observed. In clinical phase I trials, subcutaneous IL-11 was well tolerated and induced a dose-related thrombopoietic effect in women with breast cancer. IL-11 at doses of >25 μg/kg per day appeared to reduce the severity of chemotherapy-induced thrombocytopenia. In a randomized phase II trial, IL-11 at 50 μg/kg reduced the requirement for platelet transfusions as compared with that in placebo-treated controls. IL-11 is an interesting factor; however, further studies are needed to confirm its activity and are in progress.

Key words Interleukin 11 · Thrombopoiesis

Background

Interleukin 11 (IL-11) was initially cloned from the immortalized bone-marrow stroma cell line PU-34. Its gene is located on chromosome 19 and encodes a 199-amino-acid polypeptide [16]. The structure of the IL-11 protein is such that it contains no glycosylation site and has a high leucine and proline content. Similar to IL-6, IL-11 stimulates the proliferation of the T1165 plasmacytoma cell line. However, although IL-11 uses the same glycoprotein (GP) 130-mediated signal transduction pathway as IL-6, these factors act via independent receptors [18].

IL-11 exerts a synergistic effect on the proliferation of early hematopoietic stem cells when combined with other early-acting hematopoietic growth factors such as IL-3 and stem-cell factor [3, 13, 17]. Its primary activity in hematopoiesis is based upon its maturational effect on megakaryocyte precursors: it increases the ploidy of bone marrow megakaryocytes in preclinical models, producing increases in platelet production [7]. Treatment of mice with IL-11 following chemoradiotherapy results in enhanced trilineage recovery [5].

IL-11 has been shown to inhibit adipogenesis and is identical to the adipogenesis-inhibitory factor cloned by Kawashima et al. [10]. The ability of IL-11 to prolong the survival of long-term bone marrow cultures appears to be related to this adipogenesis-inhibitory activity as demonstrated by Keller et al. [12]. In this model, inhibition of adipogenesis results in the promotion of stromal cell and macrophage development. These findings may be of some importance in the treatment of bone-marrow failure states such as aplastic anemia, in which adipocytes occupy most of the bone marrow cavity.

Phase I clinical trials with recombinant human IL-11

Recombinant human IL-11 (rhIL-11) has been studied in an initial phase I trial in women with locally advanced or metastatic (stage IIIB or IV) breast cancer [8, 9]. Cohorts of at least three women were treated with doses of IL-11 ranging from 10 to 100 μg/kg per day. rhIL-11 was given by subcutaneous injection daily for 14 days during a 28-day prechemotherapy safety cycle. Following completion of the

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safety cycle, all patients received rhIL-11 for 12 days at the assigned dose after the administration of up to four 28-day cycles of cyclophosphamide at 1500 mg/m^2 per day and doxorubicin at 60 mg/m^2 per day given on day 1 of each cycle. IL-11 therapy was well tolerated at doses of ≤50 μg/kg per day. Adverse events primarily comprised reversible mild constitutional complaints, including fatigue, myalgias, and arthralgias. At no time during the course of therapy was rhIL-11 associated with fever in any patient.

All patients developed transient therapy-related anemia that was not dose-related within the first several days of treatment and that resolved within days of discontinuation of rhIL-11 administration. This appears to be due to plasma volume expansion as noted in studies by Ault et al. [2] in which normal volunteers received rhIL-11 at 25 μg/kg per day. In their study, a 25% increase in plasma volume was associated with a 15% decrease in hemoglobin concentration. This plasma volume expansion was also associated with urinary sodium retention. Similar findings have recently been reported for the anemia related to IL-6 administration [1, 14].

Prechemotherapy rhIL-11 administration induced a dose-related increase in platelets. Mean peak platelet counts of 76%, 93%, 108%, and 185% over baseline were seen in patients treated for 14 days with rhIL-11 at 10, 25, 50, and 75 μg/kg per day, respectively. A gradual increase in platelet count was seen during the 2nd week of therapy. Platelet counts were maximal following the completion of 14 days of rhIL-11 therapy. In contrast to other hematopoietic growth factors, rhIL-11 has no myeloid effect.

Dose-related increases in C-reactive protein were seen, whereas increases in other acute-phase proteins were not dose-dependent. In studies on normal volunteers [11], although rhIL-11 administration had no significant effect on platelet function, a statistically significant increase in circulating von Willebrand factor (vWF) and fibrinogen levels were noted. The multimeric pattern of the induced vWF was normal.

Studies on the effects of rhIL-11 on the bone marrow compartment reveal a statistically significant increase in the number of megakaryocytes identified morphologically on trephine biopsies at doses of ≥50 μg/kg per day [15]. Immunohistochemical evaluation with PC10, a monoclonal antibody to proliferating cell nuclear antigen (PCNA), demonstrated significant increases in the number of PCNA-positive cells (pretreatment 20.8 ± 7.8%; posttreatment 40.2 ± 14.0%; $P < 0.001$); most of these cells were erythroblasts and early myeloid precursors. This suggests that although it does not significantly affect the hematologic profile of erythroid or myeloid cells, rhIL-11 can induce a proliferative response in the early compartment. Ploidy analysis of bone marrow megakaryocytes demonstrated a maturational effect of rhIL-11 on these cells, with increases in the number of higher ploidy (64N) megakaryocytes being noted; this effect was not dose-related. No significant increase was seen in the number of assayable committed (colony-forming units-granulocyte/macrophage, burst-forming units-erythroid, or colony-forming unit-granulocyte, erythroid, macrophage, megakaryocyte or primitive (high-proliferative-potential colony-forming cell) progenitors in bone marrow or peripheral blood. Modest increases in the number of bone marrow colony-forming unit-megakaryocyte were seen in two patients treated at the highest (75 μg/kg) rhIL-11 dose.

Following chemotherapy, patients treated at the dose of 10 μg/kg per dose experienced myelosuppression (neutropenia and thrombocytopenia) similar to that seen in historical control patients. When rhIL-11 was given at doses of ≥25 μg/kg, an apparent reduction in the degree of chemotherapy-induced thrombocytopenia was seen as compared with that observed in patients treated at the lowest dose. Beyond cycle 2, patient dropout prevented conclusions being drawn regarding prevention of the development of cumulative thrombocytopenia. rhIL-11 administration had no effect on white blood cell or neutrophil count nadirs. When rhIL-11 was given together with granulocyte colony-stimulating factor, the anticipated reduction in neutropenia was seen with no unexpected toxicity.

Preliminary results of a phase I trial of rhIL-11 in women undergoing high-dose chemotherapy with bone marrow transplant demonstrate a similar safety profile [4]. In addition to constitutional symptoms, atrial arrhythmias were seen in several patients. At doses ranging from 10 to 75 μg/kg per day, rhIL-11 induced modest reductions in the duration of thrombocytopenia.

Phase II clinical trials with rhIL-11

Given the activity seen in the phase I chemotherapy study, subsequent clinical trials were designed to evaluate the activity of rhIL-11 at 25 and 50 μg/kg per day. Whereas standard phase II trials with specific chemotherapy regimens have represented the classic approach to the development of hematopoietic growth factors, rhIL-11 was developed in a novel fashion. Doses of 25 and 50 μg/kg per day were compared with placebo in a randomized, placebo-controlled, double-blind trial [6]. Patients were eligible for the study if they experienced severe thrombocytopenia (defined as a platelet count of ≤20,000/ml) and received a platelet transfusion in a given cycle of chemotherapy. This prestudy cycle was termed cycle X. Once identified, patients had to receive the identical chemotherapy regimen (no dose reduction allowed) in a subsequent study cycle termed cycle X+1. In the study cycle, patients were randomized to receive either placebo or rhIL-11 at 25 or 50 μg/kg per day starting on the day following completion of chemotherapy and continuing until the platelet count recovered to ≥100,000/ml. Patients were excluded if they were being treated for leukemia or had experienced sepsis or disseminated intravascular coagulation in cycle X.

Overall, 8/27 patients (30%) in the cohort receiving rhIL-11 at 50 μg/kg per day successfully completed therapy without requiring platelet transfusion as compared with only 1 patient (4%) in the placebo group ($P < 0.05$). Of the patients treated with rhIL-11 at 25 μg/kg per day, 18% remained transfusion-free, suggesting a dose-response re-

lationship for rhIL-11. In addition, a trend toward fewer transfusions in rhIL-11-treated patients was noted. The side effects of rhIL-11 treatment were similar to those seen in the phase I trial. A small number of patients experienced atrial arrhythmias; this was thought to be related to the plasma volume expansion and salt retention seen in these patients. For this reason, additional trials will probably incorporate a diuretic-based regimen to reduce the risk of this event. A randomized phase II trial of rhIL-11 in patients undergoing high-dose chemotherapy with peripheral blood progenitor-cell support is ongoing.

Conclusions

rhIL-11 is a new agent with the ability to stimulate platelet production. Its primary thrombopoietic mechanism of action appears to be stimulation of megakaryocyte maturation. In clinical trials it is well tolerated and is not associated with toxicities such as fever or capillary leak.

In phase I trials, doses of 25–50 μg/kg per day appeared to be well tolerated and may have reduced the degree of chemotherapy-induced thrombocytopenia. As rhIL-11 is specific for platelet production, it will need to be used with a myeloid colony-stimulating factor. In phase II trials, rhIL-11 has demonstrated the ability to reduce the risk of recurrent severe thrombocytopenia in patients previously experiencing this complication; these effects were most pronounced at a dose of 50 μg/kg per day. Phase III randomized trials comparing a dose of 50 μg/kg per day with placebo are ongoing. Data from additional trials in patients receiving high-dose chemotherapy and in the pediatric population should be available in the near future.

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