Pilot Study of Low-Dose Interleukin-11 in Patients With Bone Marrow Failure

By Razelle Kurzrock, Jorge Cortes, Deborah A. Thomas, Sima Jeha, Susan Pilat, and Moshe Talpaz

Purpose: Interleukin-11 (IL-11) is a thrombopoietic cytokine that attenuates postchemotherapy thrombocytopenia at doses of 50 μg/kg/d subcutaneously. Very little is known about the activity of IL-11 in patients with bone marrow failure states.

Patients and Methods: Our preliminary experience with IL-11 at doses of 50 μg/kg/d suggested that patients with bone marrow failure developed significant peripheral and pulmonary edema after the prolonged dosing necessary for treating these conditions. We, therefore, initiated a study of low-dose IL-11 (starting dose, 10 μg/kg/d).

Results: Sixteen patients were assessable for response. Six patients had diploid cytogenetics; the others had a variety of chromosomal abnormalities. Six (38%) of 16 patients showed a platelet response to IL-11, and two had a multilineage response (to IL-11 alone, n = 1; to IL-11 plus G-CSF and erythropoietin, n = 1). The median increase in peak platelet counts was 95 $\times$ 10^9/L above baseline in the responders (range, increase of 55 $\times$ 10^9/L to 130 $\times$ 10^9/L above baseline). Responders included five of 11 patients with myelodysplasia and one of four patients with aplastic anemia. Response durations were 12, 13, 14+, 25, 30, and 30+ weeks. Side effects of IL-11 were mild (peripheral edema, n = 7; conjunctival injection, n = 7; myalgia, n = 1; all grade 1). Seven patients had no side effects.

Conclusion: Our pilot study suggests that administration of low-dose IL-11 (10 μg/kg/d) can raise platelet counts without significant toxicity in selected thrombocytopenic patients with bone marrow failure.

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P ATIENTS WITH myelodysplasia (MDS) and other bone marrow failure states (aplastic anemia, graft failure, and so on) suffer from low platelet counts and an increased risk of serious hemorrhage.[1,2] Currently, therapeutic options in these patients are limited to platelet transfusion support. However, platelets are short-lived, and, therefore, any benefits from platelet transfusions generally last 3 days or less. Platelet transfusions are also not without side effects. For instance, such transfusions can transmit bacterial and viral infections, and, furthermore, repeated administration of platelets often results in immune refractoriness.[3,4]

To date, growth factors (granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) developed for clinical use have been successful in increasing WBC counts in patients suffering from both primary and secondary neutropenia.[5,6] In some patients with bone marrow failure, erythropoietin can increase hemoglobin and decrease RBC transfusion requirements.[5,7,8] However, little in the way of salutary effects on platelet counts have been reported. Interleukin-11 (IL-11), a molecule that stimulates megakaryocytopoiesis in rodents and monkeys, has been found to attenuate thrombocytopenia and reduce the need for platelet transfusions after myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are at high risk for severe thrombocytopenia.[9-12] The effects of this molecule in bone marrow failure states has not, however, been previously investigated.

The usual dose of IL-11 administered after chemotherapy is 50 μg/kg/d.[11] The main side effects at this dose are mild anemia and reversible arthralgia, dyspnea, edema, and tachycardia. However, tolerance is good for most patients. Our initial experience with the use of this molecule in patients who experience bone marrow failure suggested that doses between 25 and 50 μg/kg/d resulted in significant peripheral and pulmonary edema, probably because these patients require prolonged therapy (unpublished data). Therefore, we initiated a pilot study of IL-11 at low doses (10 μg/kg/d subcutaneously [SC]). Preliminary results suggest that low-dose IL-11 is biologically active and well tolerated in patients with bone marrow failure.

PATIENTS AND METHODS

Patients with bone marrow failure as a result of MDS, aplastic anemia, graft failure, or postchemotherapy aplasia were eligible for the protocol. Diagnosis was made on the basis of a review of bone marrow aspirate and biopsy and karyotype analysis. Patients could not have received chemotherapy for at least 2 months or have evidence of progressive cancer (other than worsening MDS). Patients must not have

received antithymocyte globulin for a least 3 months and not have received corticosteroids, danazol, or cyclosporine for at least 4 weeks. Other eligibility criteria included a platelet count $\leq 50 \times 10^9$/L. Patients with known allergies to *Escherichia coli*, active congestive heart failure, or documented myeloid leukemia were excluded. All patients signed informed consent in keeping with our internal review board policies.

Treatment Plan

Patients received at least two courses of IL-11. Each course consisted of 2 weeks of daily IL-11 (10 μg/kg/d SC), followed by a 2-week rest period. After the first two courses (8 weeks), patients who showed any evidence of response could continue receiving maintenance therapy. The length of the courses versus the rest period and the dose of IL-11 could be individualized during the maintenance period in accordance with patient response and side effects. In particular, dosing would be adjusted to maintain platelet counts between 150 and 450 $\times$ 10^9/L. Baseline evaluation included a complete blood cell count with differential and reticulocyte count, an ECG, and liver and kidney function tests. A bone marrow aspirate and biopsy with cytogenetic analysis was performed within 1 month before therapy. During therapy, patients were monitored with a complete blood cell count and differential and reticulocyte count three times per week for the first 6 weeks and then at least weekly. Liver and kidney function tests were repeated at least every 2 weeks, and bone marrow aspirate and biopsy were repeated at 4- to 8-week intervals.

Response Criteria

Platelet response was denoted as doubling of platelets, with platelet counts increasing to levels of more than 50×10^9/L (for patients with baseline platelet counts between 20 and 50×10^9/L) or tripling of platelets and counts increasing to levels of more than 20×10^9/L (for patients with baseline platelet counts $\leq 20 \times 10^9$/L). Baseline platelet and neutrophil counts and hemoglobin were the median of the three untransfused counts available within the 2 weeks before starting therapy. After therapy, transfused platelet counts were not considered in the evaluation of response. Patients were not administered transfusions if platelet counts were more than 10×10^9/L. By definition, patients with counts below this level had to become transfusion-independent (and untransfused platelet counts had to increase to more than 20×10^9/L) to be considered responders. Patient responses had to last at least 4 weeks while they were on therapy.

RBCs were transfused for hemoglobin ≤ 8 g/dL. Patients were considered to have an RBC response if there was an increase in hemoglobin of 2 g/dL above baseline accompanied by attainment of transfusion independence.

Neutrophil increases were considered responses if there was a tripling of neutrophils and an increase to more than $0.5 \times 10^3/\mu$L (if baseline neutrophil count was $\leq 0.5 \times 10^3/\mu$L) or a doubling of neutrophils and an increase to more than $1.0 \times 10^3/\mu$L (if baseline neutrophil counts were between 0.5 and $1.0 \times 10^3/\mu$L).

RESULTS

To date, 20 patients have been registered on trial. Sixteen patients are assessable for response. Four patients were nonassessable because they were registered in error (n = 2), noncompliant (n = 1) or received concurrent thalidomide (n = 1). All but the two patients registered in error were assessable for toxicity (n = 18).

Table 1. Patient Characteristics

	No. of Patients
Patients registered	20
Patients assessable for toxicity	18
Patients assessable for response	16
Reasons patients not assessable	
Registered in error	2
Noncompliant	1
Concurrent thalidomide	1
Age, years	
Median	58
Range	5-84
Sex	
Male	14
Female	4
Diagnosis	
RA	5
RARS	1
RAEB	5
AA	4
BMF, after auto-BMT	1
Karyotype	
Diploid	8
Insufficient metaphases	1
Monosomy 7	2
Trisomy 8	2
Monosomy 5	1
11q−	1
20q−	1
13q−	1
Trisomy 15	1
−Y	1
Baseline platelet count, $\times 10^9$/L	
Median	12
Range	1.0-48

Abbreviations: AA, aplastic anemia; BMF, bone marrow failure.

Patient Characteristics

The diagnoses of the patients included refractory anemia (RA) (n = 7), refractory anemia with ringed sideroblasts (RARS) (n = 1), refractory anemia with excess blasts (RAEB) (n = 5), severe aplastic anemia (n = 4), and bone marrow failure after autologous bone marrow transplantation (n = 1). Fourteen men and four women were treated. The median age of the patients was 58 years (range, 5 to 84 years) (Table 1). Six patients with MDS had received no prior therapy. The other patients had received one to four prior therapies (Table 2). Eight patients had diploid cytogenetics, and the other patients had a variety of chromosomal abnormalities (Table 1). The median baseline platelet count was 12×10^9/L (range, 1 to 48×10^9/L).

Responses

Six (38%) of 16 patients assessable for response showed increases in platelets (Table 3). The diagnoses of the

Table 2. Prior Therapy

Prior Therapy	No. of Patients
Antithymocyte globulin	10
Cyclosporine	9
G-CSF	5
Stem-cell factor	4
Topotecan/cytarabine	2
Allogeneic BMT	1
Amifostine	1
None	6

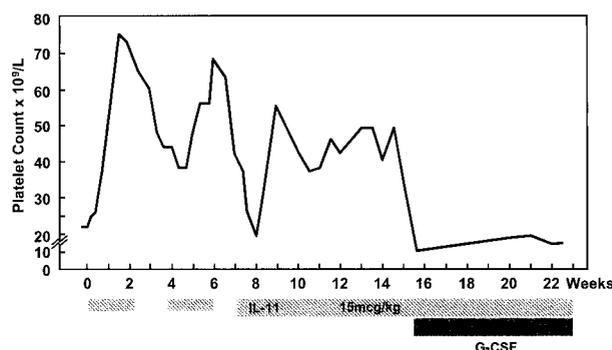Abbreviation: BMT, bone marrow transplantation.

Fig 1. Platelet response of patient no. 1. Courses of IL-11, as well as erythropoietin (EPO) and G-CSF, are depicted in the bars below the graph. IL-11 was initiated at a dose of 10 μg/kg/d and later increased to 15 μg/kg/d.

responders included RA (n = 1), RARS (n = 1), RAEB (n = 3), and aplastic anemia (n = 1). Two patients who responded had diploid cytogenetics, one had insufficient metaphases, and the other had chromosomal abnormalities, including monosomy 5 and 7, trisomy 8, and deletion of the long arm of chromosome 11 (Table 3). Response duration was 12, 13, 14+, 25, 30, and 30+ weeks.

Case no. 1. Patient no. 1 was a 66-year-old man with a diagnosis of RA of 14 months' duration. Karyotype was 46, XY, del(20q13), 11q−. Prior therapy with amifostine was unsuccessful. The initial platelet count was 22×10^9/L; hemoglobin, 9.4 g/dL; and absolute neutrophil count, 1.2×10^3/μL. The patient showed an increase in platelet counts with IL-11 administration (Fig 1); peak platelet levels were 77×10^9/L. The platelet response lasted 15 weeks. Bone marrow biopsy showed an increase in cellularity from 40% (baseline) to 70% during treatment. There was no change in the percentage of blasts or degree of dysplasia. Forty-six megakaryocytes per 10 high-power fields were seen both before and during therapy. (In normal individuals, 20 to 30 megakaryocytes are seen per 10 high-power fields. A high-power field denotes ×400 magnification.) Megakaryo-

cytes were dysplastic. At the time of loss of response, bone marrow megakaryocytes showed a decrease in number to 35 per high-power field. There was no evidence of disease progression.

Case no. 2. Patient no. 2 was a 66-year-old man with RARS of 13 months' duration. Karyotype showed insufficient metaphases. He had received no prior therapy for MDS but had been treated with a fludarabine-based regimen for previous chronic lymphocytic leukemia. His initial platelet count was 48×10^9/L, and his absolute neutrophil count was 0.9×10^3/μL. He was RBC transfusion–dependent. He showed a platelet response that lasted 14+ weeks (Fig 2); the peak platelet count was 180×10^9/L. Bone marrow biopsies showed a slight increase in cellularity during therapy (baseline cellularity, 30%; posttherapy cellularity, 50%). Bone marrow megakaryocytes increased from 21 per 10 high-power fields (baseline) to 62 per 10 high-power fields during treatment. Bone marrow dysplasia did not change significantly.

Table 3. Response to Low-Dose IL-11

	No. of Patients
Patients assessable for response	16
Responders (%)	6 (38)
Diagnosis of responders/total no. of patients	
RA	1/5
RARS	1/1
RAEB	3/5
AA	1/4
Karyotype of responders	
−5, −7, +8	1
t(3;12), 13q−	1
11q−	1
Insufficient metaphases	1
Diploid	2

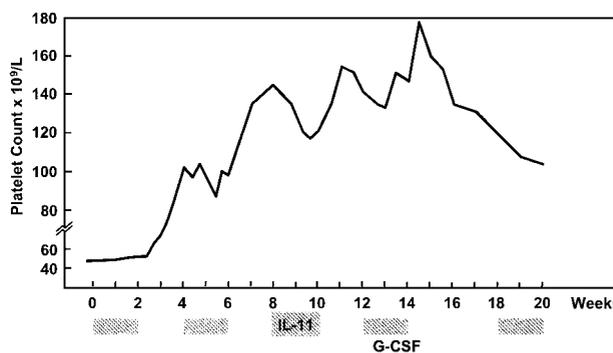NOTE. Response durations of the six patients were 12, 13, 14+, 25, 30, and 30+ weeks.

Fig 2. Platelet response of patient no. 2. Courses of IL-11 as well as G-CSF are depicted in the bars below the graph. IL-11 was administered at a dose of 10 μg/kg/d.
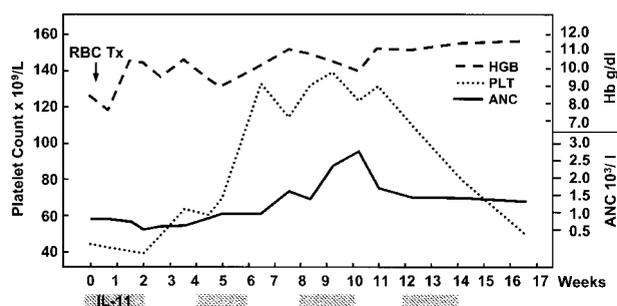
Fig 3. Platelet (PLT) response of patient no. 3. Courses of IL-11 are depicted in the bars below graph. No other growth factors were administered. IL-11 dose was 10 μg/kg/d. Because this patient had a multilineage response, hemoglobin (Hb, HGB) and absolute neutrophil (ANC) responses are depicted. Arrows represent transfusions (Tx).

Fig 4. Platelet response of patient no. 4. Courses of IL-11 as well as of EPO and G-CSF are depicted in the bars below the graph. IL-11 dose was 10 μg/kg/d.

Case no. 3. Patient no. 3 was a 56-year-old man with RAEB of 1 month's duration. Karyotype was 46, XY, t(3;12)(p10;p10), del(13q). He had a history of small cleaved lymphoma and had received an autologous transplant 5 years before development of MDS. Baseline blood counts included a platelet count of 44×10^9/L and an absolute neutrophil count of $0.9 \times 10^3/\mu$L. He was RBC transfusion–dependent. Surprisingly, he had a trilineage response to IL-11. No other growth factor was administered. Peak platelet counts were over 130×10^9/L. Hemoglobin increased to 11.5 g/dL, and the absolute neutrophil count increased to $2.5 \times 10^3/\mu$L. The response lasted 12 weeks (Fig 3). During therapy, bone marrow biopsy cellularity showed no significant changes from the baseline of 25%. At the time of peak platelet response, bone marrow blasts decreased from 17% (baseline) to 3%. At the time of loss of response, bone marrow blasts increased to 29%. However, 2 weeks later, they decreased back to baseline values without further therapy. Bone marrow megakaryocytes increased from 4 per 10 high-power fields (baseline) to 9 per 10 high-power fields during treatment. There were no significant changes in the degree of dysplasia.

Case no. 4. Patient no. 4 was a 72-year-old man with RAEB of 15 months' duration. Karyotype was diploid. He had received only supportive therapy. Baseline blood counts included a platelet count of 45×10^9/L and an absolute neutrophil count of $0.8 \times 10^3/\mu$L. He was RBC transfusion–dependent. He had a platelet response to IL-11; peak platelet counts were over 180×10^9/L. The response lasted 30 weeks (Fig 4). Bone marrow biopsy cellularity increased from 50% at baseline to 90% during therapy. Neither bone marrow blasts nor the degree of dysplasia changed significantly. Bone marrow megakaryocytes increased from 75 per 10 high-power fields (baseline) to 126 per 10 high-power fields (after therapy).
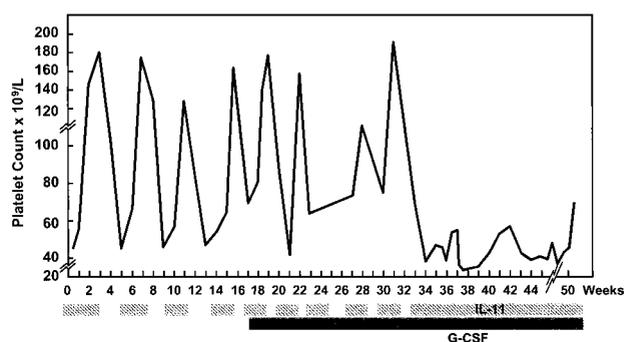
Case no. 5. Patient no. 5 was a 78-year-old man with RAEB of 3 months' duration. Karyotype showed multiple abnormalities, including monosomy 5 and 7 and trisomy 8. He had received only supportive therapy. Baseline blood counts included a platelet count of 36×10^9/L and an absolute neutrophil count of $0.9 \times 10^3/\mu$L. He was RBC transfusion–dependent. He had a platelet response to IL-11; peak platelet counts were approximately 90×10^9/L. The response lasted 25 weeks (Fig 5). Bone marrow biopsy cellularity remained at approximately 50% to 60% throughout therapy. Neither bone marrow blasts nor the degree of dysplasia changed significantly. Bone marrow megakaryocytes did not change from baseline levels of approximately 26 per 10 high-power fields.

Case no. 6. Patient no. 6 was a 58-year-old woman with severe aplastic anemia of 3 years' duration. Karyotype was diploid. Prior therapy included antithymocyte globulin and cyclosporine, as well as stem-cell factor and G-CSF. Baseline blood counts included a platelet count of 1.0×10^9/L and an absolute neutrophil count of $0.6 \times 10^3/\mu$L (while receiving G-CSF). She was RBC transfusion–dependent. She had pre-
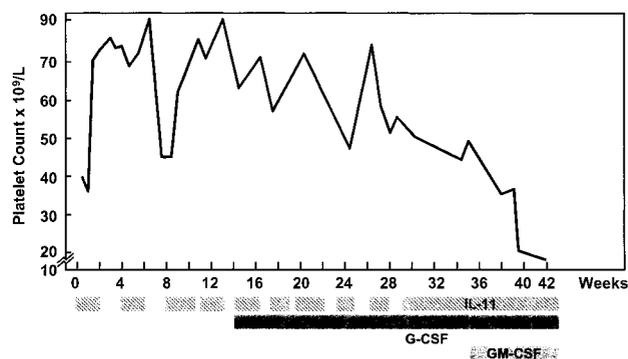

Fig 5. Platelet response of patient no. 5. Courses of IL-11 as well as of EPO, G-CSF, and GM-CSF are depicted in the bars below the graph. IL-11 dose was 10 μg/kg/d.
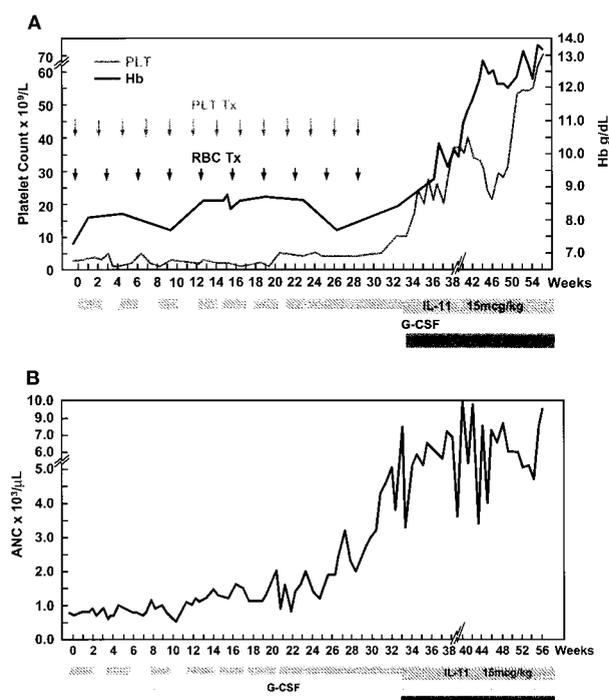
Fig 6. Platelet response of patient no. 6. Bars below graphs depict courses of IL-11, EPO, and G-CSF. Initial IL-11 dose was 10 μg/kg/d; later increased to 15 μg/kg/d. Hemoglobin (A) and ANC (B) response are shown. Arrows represent transfusions.

viously received G-CSF together with stem-cell factor for close to 1 year without a major response in any lineage (including neutrophils). During IL-11 therapy, G-CSF (300 μg/d SC) was continued. All three lineages began to increase after approximately 20 weeks on therapy (at which time the rest period between courses had been discontinued). At 34 weeks, the IL-11 dose was increased from 10 to 15 μg/kg/d SC, and erythropoietin at a dose of 10,000 units SC (three times per week) was added. At this point, blood counts began to increase more rapidly. Peak platelet counts were over 100×10^9/L. Hemoglobin increased to 13.5 g/dL, and absolute neutrophil counts increased to 9.0×10^3/μL. Response duration was 30+ weeks (Fig 6). Bone marrow biopsy cellularity increased from 5% at baseline to 60% during therapy. Neither bone marrow blasts nor the degree of dysplasia changed significantly. Bone marrow megakaryocytes increased from 2 per 10 high-power fields to 11 per 10 high-power fields.

Side Effects

Patient tolerance of low-dose IL-11 was excellent. Seven patients developed peripheral edema, seven showed conjunctival injection, and one complained of myalgias. These toxicities were mild (grade 1). Two patients were given furosemide (20 mg by mouth daily) for mild peripheral edema. Seven patients had no side effects.

DISCUSSION

Bone marrow failure states include a variety of conditions, such as MDS, aplastic anemia, and iatrogenic (chemotherapy-induced) prolonged pancytopenias. In general, G-CSF and GM-CSF can successfully increase neutrophil counts in MDS patients.[5,6,13-31] For some time, the interest in myeloid growth factors was tempered by the concern that their usage led to early transformation. Controlled studies with G-CSF and GM-CSF have refuted this notion.[14-16,18,21,23] However, less than 20% of MDS patients will have a salutary response to erythropoietin,[7,32-42] and platelet responses after growth factor therapy are reported only anecdotally.

Although MDS is a preleukemic state, most patients suffer from and often succumb to the sequelae of cytopenias, without overt progression to leukemia.[1] Management of MDS has included the use of differentiating agents and chemotherapy. Many of these trials have been unrewarding or have yielded excessive toxicity, and a positive impact on survival has not been demonstrated. Aplastic anemia is treated most successfully with bone marrow transplantation or immunosuppression with antithymocyte globulin and cyclosporine.[2] However, for patients who lack sibling donors and do not respond to immunosuppression, there are few options.[43] Graft failure complicates a significant minority of bone marrow transplants. As with other bone marrow failure states, G-CSF and GM-CSF can improve neutrophil counts, but no molecule has proven efficacious at increasing platelet counts. Therefore, for all these cytopenic states, there has been an ongoing interest in the potential beneficial effects of platelet growth factors.

IL-11 is a thrombopoietic cytokine that promotes the growth of hematopoietic stem cells and megakaryocytic progenitors and induces megakaryocyte differentiation, which results in increased platelet counts in animal models of compromised hematopoiesis and in cancer patients after chemotherapy.[9-12] IL-11 administered to mice undergoing bone marrow transplantation after total-body irradiation stimulates platelet and neutrophil recovery.[10] When stem-cell factor is also administered, increases in all three lineages without toxicity is observed. In humans, several studies have demonstrated that IL-11 attenuates chemotherapy-induced thrombocytopenia.[11,44] Currently, IL-11 is the only molecule approved in the United States for ameliorating thrombocytopenia.

The current trial represents the first study of IL-11 for patients in bone marrow failure states. The approved dose of IL-11 postchemotherapy is 50 μg/kg/d SC. In general,

this dose is reasonably well tolerated when administered for the short periods (approximately 7 days) needed after chemotherapy. However, our preliminary experience suggested that the prolonged dosing required in patients with bone marrow failure resulted in significant fluid accumulation when 25 to 50 μg/kg was administered daily (unpublished data). Therefore, we initiated a pilot trial of low-dose IL-11 (10 μg/kg/d). The major objectives of this trial were to ascertain whether these low doses of IL-11 were biologically active and tolerable. Six (38%) of 16 patients showed significant increases in platelet counts (Figs 1 to 6). In most of these patients, platelets increased with the first 2-week course of IL-11. In patients no. 1 and 4, abrupt decreases in platelet counts were seen in the 2-week rest period between courses (Figs 1 and 4). In four patients, significant increases in bone marrow megakaryocytes accompanied the platelet responses. Interestingly, one patient (case no. 3, Fig 3) showed a multilineage response to IL-11 given without any other concomitant growth factor. This is not totally surprising, because IL-11 can influence primitive hematopoietic cell development.[45] One patient (case no. 6) with severe aplastic anemia (initial platelet count, $1.0 \times 10^9/L$) showed a multilineage response when IL-11 was combined with G-CSF and erythropoietin. This patient was unusual in that, previous to IL-11 therapy, she had remained severely neutropenic while on G-CSF. Furthermore, the time to response was approximately 20 weeks. We have noted a similar delay in time to response when severe aplastic anemia patients were treated with other growth factors, eg, IL-3/GM-CSF combinations or stem-cell factor.[46,47] In fact, the median time to initial response in our aplastic anemia patients receiving stem-cell factor was 4 months.[47] Alternatively, it may have been a change in the schedule or dose of IL-11 administration that was critical to response. Improvement in platelet counts started when the 2 weeks on/2 weeks off schedule of IL-11 was replaced by continuous administration (Fig 5). The multilineage response was observed several weeks later, when the dose of IL-11 was increased from 10 to 15 μg/kg/d and erythropoietin was added. Bone marrow megakaryocytes and cellularity also increased significantly in this patient.

Several patients eventually ceased to respond. Bone marrow follow-up showed that end of platelet response was not accompanied by other indications of progressive disease, such as transformation to leukemia. Future studies are planned to monitor for development of neutralizing IL-11 antibodies.

Several other thrombopoietic molecules have also been administered to patients with bone marrow failure, with variable results. Thrombopoietin was administered to patients with graft failure without significant therapeutic benefit, albeit in a study that allowed only one to five doses of this molecule monthly.[48] IL-3 has shown limited thrombopoietic activity in patients with aplastic anemia or MDS,[13,49] although multilineage responses have been seen when IL-3 is combined with GM-CSF.[46] Stem-cell factor has also demonstrated multilineage responses in some patients with aplastic anemia.[47] Finally, IL-6 has been reported to have thrombopoietic activity in MDS, albeit with significant toxicity.[50-52] To date, none of the above molecules have demonstrated benefits leading to their approval for any clinical indication in the United States, although some of these molecules (eg, stem-cell factor) have been approved in other countries for indications such as stem-cell mobilization.

Taken together, the data in the literature as well as our pilot study suggest that several cytokines are able to increase platelet counts in subsets of patients experiencing bone marrow failure. Some of these patients may have multilineage responses, especially if combinations of growth factors are used. Our current study demonstrates that IL-11 is biologically active in bone marrow failure states at considerably lower doses than previously used after chemotherapy. At these doses, this molecule is capable of increasing platelet counts in a subset of patients with bone marrow failure without significant toxicity. Because some of the responses were short-lived and occurred in patients with only mild thrombocytopenia, the clinical significance of this biologic activity remains to be ascertained in patients who are transfusion-dependent. Further studies are needed to explore a variety of issues: (1) other schedules of administration (eg, alternate day, high-dose once weekly, and others), (2) combinations of IL-11 with other growth factors or with other treatments, (3) biologic or phenotypic characteristics that correlate with response, (4) mechanisms of response and loss thereof, (5) importance of duration of therapy, especially in patients with severe thrombocytopenia, and (6) overall impact on larger numbers of patients who are platelet transfusion–dependent.

ACKNOWLEDGMENT

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