original contribution

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An Open-Label Pilot Study to Evaluate a Flexible Dosing Regimen of Epoetin Alfa for the Treatment of Chemotherapy-Induced Anemia: 60,000 Units Weekly Followed by 60,000 Units Every 2 Weeks

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Abstract

Purpose: This open-label, single-arm pilot study assessed the safety and efficacy of administering an initial epoetin alfa dose of 60,000 U subcutaneously once weekly (initial dosing phase [IDP]) followed by an extended dose regimen of 60,000 U subcutaneously every 2 weeks (extended dosing phase [EDP]). **Patients and Methods:** Patients who had a hematologic response, defined as hemoglobin (Hb) level increase ≥ 1 g/dL from week 1 baseline at any time during the 4-week IDP (the primary efficacy endpoint), were eligible to enter the EDP at week 5 and receive every-other-week treatment for up to 12 additional weeks. Patients who did not exhibit this increase in the IDP were withdrawn. **Results:** Fifty-one patients were enrolled; the mean baseline Hb level was 10.1 g/dL ± 0.79 g/dL. Thirty-three patients (64.7%) met the primary efficacy endpoint of Hb increase ≥ 1 g/dL during the IDP; 29 patients (56.9%) proceeded to the EDP. Mean Hb level at entry to the EDP was 12.4 g/dL ± 0.99 g/dL. Further Hb increase in the EDP (average Hb level ≥ week 5 Hb value) was achieved in 12 of 29 patients (41.4%). Final Hb value for patients in the EDP was 11.7 g/dL ± 1.28 g/dL. Four patients received a total of 5 red blood cell transfusions during the study. Epoetin alfa was well tolerated and had a safety profile similar to that observed with labeled dosing. Two patients experienced a clinically relevant thrombotic vascular event. **Conclusion:** Results from this pilot study suggest that higher initial weekly dosing of epoetin alfa followed by extended dosing is safe and effective for treating chemotherapy-induced anemia.

Introduction

It has been well established that epoetin alfa safely and effectively treats anemia in patients with cancer who are receiving chemotherapy.[1-5] Dosing frequencies investigated in these studies included once-weekly fixed dosing (40,000 U) as well as 3-times-weekly weight-based dosing (150 U/kg) or fixed

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dosing (10,000 U). However, there are limited data available regarding the administration of extended dosing regimens of epoetin alfa after response to initial weekly dosing. Results from several studies have demonstrated the feasibility of successfully managing chemotherapy-induced anemia with initial weekly epoetin alfa doses of 40,000 U or 60,000 U, followed by extended dosing every 2 weeks with 60,000 U[6] or every 3 weeks with 80,000 U[7] or 120,000 U.[8,9] The various epoetin alfa dosing regimens used in these studies produced similar results in terms of increases in hemoglobin (Hb) during initial dosing and maintenance of Hb during extended dosing.

Recent pharmacokinetic data have shown the circulating half-life of epoetin alfa to vary among patient populations. In contrast to the chronic renal failure setting, in which the circulating half-life ranges from 4 hours to 13 hours after intravenous administration, the circulating half-life of epoetin alfa in patients with chemotherapy-induced anemia is considerably longer, averaging 40 hours (range, 16-67 hours) with doses of 150 U/kg 3 times weekly or 40,000 U weekly administered subcutaneously.[10,11] This might be caused by differences in the cellularity of bone marrow or its capability of clearing epoetin alfa under the influence of chemotherapy. The precise relationship between epoetin alfa half-life and its pharmacodynamic activity in stimulating the production of red blood cells is still unclear.

Extending the dosing interval for epoetin alfa beyond once weekly would provide added flexibility for patients and medical staff and could improve compliance. An every-2-week epoetin alfa dosing regimen would also allow physicians to schedule erythropoietic therapy to coincide with various dose-dense chemotherapy regimens. The present study evaluated the hematologic response to initial epoetin alfa dosing of 60,000 U weekly for a fixed 4-week period, followed by extended dosing of 60,000 U every 2 weeks, in anemic patients with cancer receiving chemotherapy.

Patients and Methods

Inclusion/Exclusion Criteria

Anemic (Hb ≤ 11 g/dL) patients aged ≥ 18 years with a histologically confirmed nonmyeloid malignancy were eligible for enrollment if they were to receive chemotherapy for a minimum of 12 weeks and had a life expectancy of ≥ 6 months, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, platelet count ≥ 100,000/μL, and serum creatinine level ≤ 1.5 mg/dL. Patients were excluded from study participation if they had received any erythropoietic agent within 3 months, if they had anemia caused by factors other than cancer or chemotherapy, if they had received a red blood cell transfusion within 28 days, or if radiation therapy was planned during the study. Also excluded were patients who had untreated central nervous system metastases; uncontrolled hypertension or a history of uncontrolled cardiac arrhythmias, pulmonary embolism, or venous or arterial thrombosis; poorly controlled seizures; or any unstable medical condition. Approval of the study was obtained from the institutional review board for each site, and written informed consent was obtained from each patient before the start of the study.

Study Design and Treatment

This was an open-label, single-arm, multicenter pilot study conducted at 13 sites in the United States. The treatment period was divided into 2 phases: an initial dosing phase (IDP) of weekly dosing followed by an extended dosing phase (EDP) of every-2-week dosing. The IDP encompassed 4 weekly visits (weeks 1-4); at each visit, a 60,000-U subcutaneous epoetin alfa dose was to be administered. Patients who exhibited an Hb level increase ≥ 1 g/dL compared with their week 1 baseline level at any time during the IDP (change from week 1 baseline level at weeks 2, 3, 4, or 5) were eligible to enter the EDP at week 5. Patients entering the EDP were treated with epoetin alfa 60,000 U subcutaneously every 2 weeks for a period of up to 12 additional weeks (doses to be administered at weeks 5, 7, 9, 11, 13, and 15). Patients who did not exhibit a ≥ 1-g/dL Hb increase during the IDP (IDP nonresponders) were to be withdrawn from the study, as were patients who had a decrease in Hb of ≥ 2 g/dL after entering the EDP (EDP nonresponders). If Hb increased to > 13 g/dL at any time during the study, study drug was withheld until Hb was ≤ 12 g/dL and was then resumed at a reduced dose of 40,000 U. In addition, the dose was reduced from 60,000 U to 40,000 U in either dosing phase for Hb rate of increase > 1.3 g/dL in a 2-week period, as per the epoetin alfa labeling at the time of study initiation. No dose escalation was allowed during the study. To avoid depletion of available iron stores and to adequately support erythropoiesis, all patients were to receive oral ferrous sulfate 325 mg daily or an equivalent preparation, as tolerated. Patients were transfused as deemed medically necessary by the investigator. Patient participation could be terminated before study completion for any of the following reasons: an adverse event (AE), disease progression with cessation of chemotherapy, noncompliance with the study protocol, discontinuation of chemotherapy before 12 weeks on study, or at the request of the patient, investigator, or sponsor.

Study Assessments

Patients were screened for study eligibility at a screening visit that occurred ≤ 14 days before treatment with epoetin alfa, with the exception of the complete blood count and serum pregnancy test, which were to occur within 3 days and 7 days before treatment, respectively. Demographic information, medical history, previous and concomitant medications, and transfusion history were collected at the screening visit, as were findings from the following procedures: physical

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examination, ECOG performance status, tumor assessment, vital signs, and laboratory data (including complete blood count with differential, serum pregnancy test, iron profile, and serum chemistry panel). Serum antierythropoietin antibody testing was to be conducted at week 1 baseline, before the administration of epoetin alfa, and at study completion or early withdrawal. Additional serum samples were to be collected if pure red cell aplasia or loss of effect of epoetin alfa in the treatment of anemia was suspected during the course of the study. Vital signs (including blood pressure) and complete blood count were monitored weekly.

Efficacy Assessments

The primary efficacy endpoint was the proportion of patients exhibiting hematologic response, defined as Hb increase ≥ 1 g/dL from week 1 baseline at any time during the IDP (up to week 5). The secondary efficacy endpoint was the proportion of patients in whom further Hb increase occurred during the EDP (EDP average Hb ≥ week 5 Hb value). Two categories of EDP Hb increase were assessed: EDP average Hb ≥ 1 g/dL higher than the week 5 Hb value and EDP average Hb 0-0.9 g/dL higher than the week 5 Hb value. Additional outcomes assessed were the mean Hb change from baseline by study week and the proportion of patients receiving red blood cell transfusions throughout the entire study.

Safety Assessments

Adverse events were recorded throughout the study. All AEs and serious AEs (SAEs) were reported, beginning with the first study-related procedure and until 30 days after the last study-related procedure. Any AE or SAE that was ongoing was followed for 90 days after the last study-related procedure or until resolution, whichever came first. Adverse events reported in the study were coded using the Medical Dictionary for Regulatory Activities,® version 6.0. Thrombotic vascular events (TVEs) were classified using a sponsor-developed dictionary that contained specific Medical Dictionary for Regulatory Activities®–preferred terms. The dictionary further classified TVEs as clinically relevant if the terms were determined by the sponsor to be life-threatening or serious and included the following: myocardial infarction or ischemia; embolism, including pulmonary embolism; deep venous thrombosis; cerebral ischemia or infarction; left ventricular failure; or thrombotic microangiopathy. Terms not considered clinically relevant included superficial thrombophlebitis, catheter-related thrombotic events, chest pain, thrombosis not treated with anticoagulation, and events that could, but not necessarily would, be caused by an underlying TVE. All patients experiencing AEs, including TVEs, received treatment according to standards of care as determined by the investigator. Investigators were responsible for assigning causality of all AEs to study drug and for determining whether the patient should be withdrawn from the study.

Statistical Analysis

Continuous variables were summarized by mean and standard deviation; categoric variables were summarized by frequency and percentage. All efficacy and safety analyses were performed on the modified intent-to-treat (ITT) population, defined as all patients enrolled and treated with ≥ 1 dose of study medication. For hematologic response analyses, Hb values were set to missing if they were obtained within 28 days after a red blood cell transfusion. The last-value-carried-forward method was used to impute a patient's missing final Hb value only; no other values were imputed. Efficacy analyses were also conducted on the subset of patients who remained transfusion free on study (transfusion-free modified ITT population).

Results

Patient Demographics

Fifty-one patients were enrolled at 13 sites between September 2003 and April 2004. All enrolled patients received ≥ 1 dose of study medication (modified ITT and safety populations). Among these 51 patients, 5 had baseline Hb values in the range of 11.1-11.9 g/dL (a deviation of < 10% from the study entry criterion). For these patients, screening Hb values were in the eligible range; however, the first dose of study drug was given before obtaining the results of the baseline Hb assessment.

Demographic and baseline characteristics are provided in Table 1. The mean age was 65.6 years; mean Hb level was 10.1 g/dL ± 0.79 g/dL. More women than men were enrolled, and most of the patients were white. Most patients had a baseline ECOG performance status of 0/1. The majority of patients had solid tumors. The most common solid tumor sites were breast, colorectum, and lung. Of the 44 patients with solid tumors, 58.1% had metastatic disease. There were no clinically noteworthy findings among the baseline chemistry parameters.

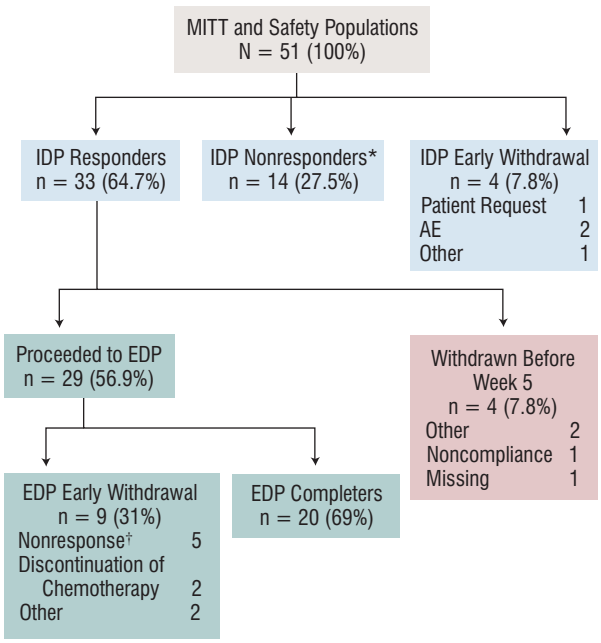
Initial Dosing Phase (60,000 U Weekly)

Dosing. All 51 patients received the initial dose of 60,000 U as planned. In the IDP, 10 of 51 patients (19.6%) had ≥ 1 dose withheld (for Hb > 13 g/dL), and 12 of 51 patients (23.5%) had ≥ 1 dose reduction (after dose withheld for Hb > 13 g/dL or for Hb rate of increase > 1.3 g/dL in a 2-week period). Mean dose in this phase was 58,268 U weekly.

Efficacy Assessments. The primary efficacy endpoint (proportion of patients achieving hematologic response, defined as Hb increase ≥ 1 g/dL from week 1 baseline at any time during the IDP) was achieved by 33 patients (64.7%). The mean time to response during the IDP was 15.5 days ± 6.7 days.

Figure 1

Patient Disposition



*IDP nonresponders are defined as patients whose Hb level did not increase by ≥ 1 g/dL compared with baseline in this phase (ie, not eligible for EDP).
†EDP nonresponders are defined as patients whose Hb level decreased by ≥ 2 g/dL after beginning EDP dosing.

Table 1

Demographics and Baseline Characteristics (N = 51)

Characteristic	Value (%)
Age, Years (Mean ± SD)	65.6 ± 11.1
Sex	
Male	19 (37.3)
Female	32 (62.7)
Ethnicity	
White	40 (78.4)
Hispanic/Latino	5 (9.8)
Black	4 (7.8)
Asian/Pacific Islander	2 (3.9)
ECOG Performance Status	
0	17 (33.3)
1	27 (52.9)
2	7 (13.7)
Tumor Type	
Hematologic	7 (13.7)
Solid	44 (86.3)
Solid Tumor Site*	
Breast	10 (22.7)
Colorectal	9 (20.5)
Lung	9 (20.5)
Other	16 (36.4)
Baseline Hemoglobin, g/dL (Mean ± SD)	10.1 ± 0.79
Baseline Iron, μmol/L (Mean ± SD)	12 ± 7.88
Baseline Transferrin Saturation, % (Mean ± SD)	23.3 ± 14.3

*n = 44.
Abbreviation: SD = standard deviation

Extended Dosing Phase (60,000 U Every 2 Weeks)

Dosing. Of the 51 patients in the IDP, 29 (56.9%) advanced to the EDP (every-2-week dosing; Figure 1). Twenty of 29 patients (69%) who entered the EDP had ≥ 1 dose withheld during this phase (for Hb > 13 g/dL). An identical number of patients (20 of 29; 69%) had ≥ 1 dose reduction during the EDP (after dose withheld for Hb > 13 g/dL or for Hb rate of increase > 1.3 g/dL in a 2-week period). Mean dose administered in this phase was 45,790 U every 2 weeks.

Efficacy Assessments. The secondary efficacy endpoint was the proportion of patients in whom further Hb increase occurred during the EDP (average Hb ≥ week 5 Hb value). The mean Hb level at the start of the EDP (week 5) was 12.4 g/dL ± 0.99 g/dL. Twelve (41.4%) of the 29 patients who entered the EDP exhibited further Hb increase; 2 patients (6.9%) exhibited EDP average Hb ≥ 1 g/dL greater than the week 5 Hb value, and 10 patients (34.5%) exhibited EDP average Hb 0-0.9 g/dL higher than the week 5 Hb value. For the 17 patients not exhibiting further Hb increase during the EDP, Hb decreased by a mean of –1 g/dL ± 0.6 g/dL during this phase. Five patients (17.2%) had a decrease in Hb of ≥ 2 g/dL after entering the EDP and were withdrawn from the study. For the 29 total patients participating in the EDP, the mean final Hb value was 11.7 g/dL ± 1.28 g/dL.

Both Phases

Additional assessments included mean Hb level change over time and the proportion of patients requiring red blood cell transfusion. The mean Hb level increased approximately 2 g/dL from baseline by week 6 and was then fairly stable throughout the remainder of the study (Figure 2). Four patients received a total of 5 red blood cell transfusions during the study. Three red blood cell transfusions were

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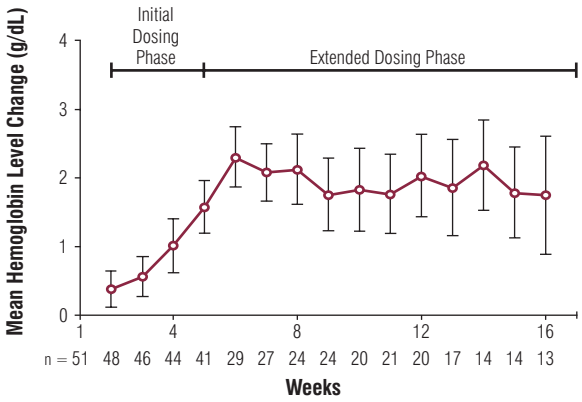
Figure 2

Mean Change in Hemoglobin Level from Baseline Level by Study Week



Bars represent 95% confidence intervals.

administered during weeks 1-4, 1 during weeks 5-8, and 1 during weeks 9-12. Efficacy analyses were also performed on the subset of patients who remained transfusion free on study (n = 47); the results were similar to those of the modified ITT population (n = 51).

Safety Assessments

All 51 patients were evaluable for safety. The majority (94.1%) of patients experienced ≥ 1 AE. The most commonly reported AEs were nausea (23.5%), asthenia (21.6%), and fatigue (21.6%). Most AEs were considered by the investigators to be unrelated to study drug. Thirteen patients (25.5%) experienced ≥ 1 SAE during the study. Two patients (3.9%) each experienced a single clinically relevant TVE during the study, both during the IDP of weekly dosing. One patient experienced deep venous thrombosis on study day 1, and a second patient experienced chest pain on study day 25. In both cases, the investigator assessed the event as not related to study drug. Three patients (5.9%) died during the study: 2 from disease progression and 1 from sepsis.

Changes over time in hematocrit and red blood cell count levels were consistent with the change observed in Hb. The mean final white blood cell and platelet counts were not significantly different from the counts obtained at week 1 baseline. Individual changes in laboratory parameters were as expected for this patient population. Assay results for antierythropoietin antibodies were negative for the 32 patients who were tested at baseline and the 24 patients who were tested at study completion or early withdrawal. The mean changes in systolic and diastolic blood pressure over time were not clinically meaningful.

Of the 45 patients who had final ECOG performance status assessed, the majority (39; 86.7%) had an ECOG performance status of 0/1. Of the 25 patients for whom tumor response data were available at the final study visit, 3 were noted to have progressive disease (compared with 12 patients noted to have progressive disease of 26 evaluated at the screening visit).

Discussion

Use of an extended dosing regimen of epoetin alfa after initial Hb response with weekly dosing is a viable option for anemic patients with cancer who are receiving chemotherapy. Less frequent administration of therapy might sustain Hb increases and provide greater flexibility in dosing options. In this pilot study, the majority of patients (64.7%) exhibited a ≥ 1-g/dL increase in Hb with an initial dose of 60,000 U weekly during the 4-week IDP. This is comparable with response rates achieved in other open-label studies of 60,000 U weekly initial dosing[6,7] and with response rates achieved in studies of 40,000-U weekly initial dosing with potential escalation to 60,000 U weekly.[4,5,12] Moreover, of the 29 patients who entered the EDP in this study, 12 patients (41%) exhibited further Hb increase with 60,000 U every-2-week dosing. Mean Hb level at week 5 for the 29 patients participating in the EDP was 12.4 g/dL; mean final Hb level for these patients was 11.7 g/dL. These data demonstrate that every-2-week dosing with epoetin alfa 60,000 U can successfully maintain an initial Hb response within the target Hb range for erythropoietic therapy as set forth by the National Comprehensive Cancer Network.[13]

Data are now available from a number of studies investigating various extended dosing regimens for epoetin alfa in patients with cancer who are receiving chemotherapy.[6-9] Dose regimens used in these trials include initial dosing with 60,000 U weekly followed by 60,000 U every 2 weeks,[6] initial dosing with 60,000 U weekly followed by 80,000 U every 3 weeks,[7] initial dosing with 60,000 U weekly followed by 120,000 U every 3 weeks,[8] and initial dosing with 40,000 U weekly followed by 40,000 U weekly or 120,000 U every 3 weeks.[9]

In studies conducted by Montoya et al[7] and Gregory et al,[6] epoetin alfa was administered at 60,000 U weekly initially to a target Hb level of 12 g/dL, followed by 80,000-U every-3-week dosing[7] or 60,000-U every-2-week dosing.[6] Final data from these trials show that hematopoietic response (Hb ≥ 12 g/dL or Hb increase ≥ 2 g/dL compared with baseline) in the IDP was exhibited by 73% and 65% of patients, respectively. Slightly > 60% of patients in each study entered into the EDP, with average Hb levels at EDP entry of approximately 12 g/dL. Proportions of patients maintaining an average Hb between 11 g/dL and 12.5 g/dL were 74%[7] and 60.7%[6] over an average EDP treatment duration of 9.8 weeks and 13.2 weeks, respectively.

A pilot trial by Patton et al assessed the effects of an extended epoetin alfa dosing regimen in 20 anemic (Hb ≤ 11 g/dL) patients with cancer receiving chemotherapy.[8] Epoetin alfa administered at 60,000 U weekly resulted in mean Hb level increases of 1 g/dL ± 1.1 g/dL by week 4 and 2.9 g/dL ± 1.9 g/dL by week 8 (excluding patients who received transfusion during the study). The mean Hb level was maintained at approximately 13 g/dL in the 13 patients who went on to receive therapy of 120,000 U every 3 weeks.

A phase III trial by Steensma et al investigated 2 different maintenance dosing schedules of epoetin alfa in patients with cancer-associated anemia (N = 365).[9] Patients were randomly assigned at enrollment to receive 40,000 U weekly or 120,000-U every-3-week maintenance dosing, with all patients initially receiving 3 doses of 40,000 U weekly. Mean Hb change during the study was statistically significantly greater in patients randomized to receive weekly maintenance dosing, compared with patients randomized to receive every-3-week maintenance dosing (1.8 g/dL vs. 1.4 g/dL; $P = 0.0097$); however, the clinical importance of this Hb difference is unclear. The weekly dosing group did, however, also experience a statistically significantly greater rate of doses withheld for Hb level > 13 g/dL (61% vs. 36%; $P < 0.0001$). Less frequent dosing intervals might mean fewer dosage adjustments and interruptions and, also, gradual Hb level changes that are associated with more acceptable rates of increase. A small number of studies have raised the possibility of inferior treatment outcomes when patients are treated with erythropoietic agents to Hb levels > 13 g/dL.[14,15]

The epoetin alfa dosing regimen evaluated in the present study was well tolerated. Only 2 patients (3.9%) experienced a clinically relevant TVE, both during the IDP of weekly dosing. This is similar to the rate seen in a placebo-controlled trial conducted by Witzig et al, in which the incidence of TVEs for patients randomized to the 40,000 U weekly epoetin alfa arm was 5%.[5] Gregory et al and Montoya et al reported somewhat higher rates of clinically relevant TVEs: 11.6% and 9.6%, respectively.[6,7] A randomized, open-label study of epoetin alfa initiated at 40,000 U weekly or 80,000 U every 2 weeks reported a clinically relevant TVE rate of 8% for both treatment groups.[16]

Conclusion

The dosing regimen investigated in this pilot study (60,000 U weekly followed by 60,000 U every 2 weeks) effectively increased and maintained Hb levels. The AE profile was consistent with that expected for this patient population. To date, the great majority of epoetin alfa extended dosing studies in chemotherapy-induced anemia, including the study reported here, have used a weekly IDP followed by an every-2-week or every-3-week EDP. Expanding the range of available dosing regimens for epoetin alfa has the advantage of improved flexibility for patients and clinicians, while still maintaining the hematologic benefits of treatment. Based on the results of this and other studies in patients with chemotherapy-induced anemia, the investigation of extended epoetin alfa dosing intervals at initiation of therapy is warranted.

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