Key words: Erythropoietin, Flexible dosing, Hemoglobin

original contribution

A Pilot Study to Evaluate the Safety and Clinical Outcomes of Once-Weekly Epoetin Alfa 80,000 U in Anemic Patients with Cancer Receiving Chemotherapy

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Abstract

Background: Epoetin alfa is indicated for the treatment of chemotherapy-induced anemia at doses of 150 U/kg 3 times weekly or 40,000 U once weekly. Higher starting doses may lead to higher hematologic response rates (RRs), earlier hematologic responses, and earlier identification of nonresponders. The hematologic response and safety of epoetin alfa at a starting dose of 80,000 U once weekly in anemic patients (hemoglobin [Hb] ≤ 11 g/dL) with nonmyeloid malignancies receiving chemotherapy were evaluated in this open-label, multicenter pilot study. **Patients and Methods**: Epoetin alfa was initiated at 80,000 U once weekly and reduced if Hb increased to > 13 g/dL or increased > 1.3 g/dL in a 2-week period during the 12-week study. The primary efficacy endpoint was major hematologic response (Hb increase ≥ 2 g/dL or Hb ≥ 12 g/dL, independent of transfusion). Secondary endpoints were minor hematologic response (Hb increase ≥ 1 g/dL but < 2 g/dL) and incidence of transfusions. **Results**: Of 69 patients enrolled, 47 (68%) completed the study. A majority of patients (72%) exhibited a major hematologic response with epoetin alfa 80,000 U once weekly. Mean Hb levels increased by 2.2 g/dL from baseline after 12 weeks of therapy. Six patients (8.8%) received packed red blood cell transfusions during the study. The dose of epoetin alfa was reduced, or held then reduced, per protocol in 48 patients (69.6%). Ten patients (14.5%) in the safety population experienced a total of 11 clinically relevant thrombotic vascular events. **Conclusion**: Epoetin alfa at a starting dose of 80,000 U once weekly (with appropriate dose reductions) increased Hb level, was associated with a packed red blood cell transfusion rate < 5% after 4 weeks of therapy, and was safe and generally well tolerated in anemic patients with cancer receiving chemotherapy. The hematologic RR, however, was not markedly improved compared with previous trials with 40,000-60,000 U once weekly, perhaps partly because of the high frequency of dose reductions.

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Weekly Epoetin Alfa 80,000 U in Cancer Patients

Introduction

Anemia is common in patients with cancer and can be caused by the myelosuppressive effects of chemotherapy or radiation therapy or by the disease itself. Mild to moderate anemia (hemoglobin [Hb] level, 8-12 g/dL) has been reported in up to 75% of patients with cancer receiving chemotherapy and/or radiation therapy.[1] Anemia secondary to cancer therapy is associated with numerous clinical consequences, including fatigue, dyspnea, palpitations, tachycardia, asthenia (muscle weakness), anorexia, general weakness, and cognitive dysfunction, all of which contribute to a notable reduction in patient quality of life.[2] Therefore, aggressive treatment of anemia is an important and warranted aspect of cancer therapy. The method used to manage the anemia resulting from myelosuppressive chemotherapy depends on its severity and includes crystalloid treatment, iron replacement, red blood cell transfusion, administration of erythropoietic agents, or a combination of options.[3]

Within the past decade, recombinant erythropoietic agents have become widely used for the treatment of mild to moderate anemia resulting from chemotherapy. Large, open-label, community-based studies and randomized, placebo-controlled clinical trials have demonstrated that recombinant human erythropoietin (r-HuEpo; epoetin alfa) at doses of 150 or 300 U/kg (10,000 or 20,000 U) administered 3 times weekly or 40,000 or 60,000 U administered once weekly significantly increases Hb levels, reduces transfusion requirements, and improves quality of life in anemic patients with nonmyeloid malignancies who are receiving chemotherapy.[4-10] Several clinical trials have also demonstrated that darbepoetin alfa increases Hb levels and reduces red blood cell transfusions when administered once weekly or every 2 weeks in patients with chemotherapy-induced anemia.[11-14] Both agents were well tolerated, with the majority of adverse events (AEs) attributable to concurrent chemotherapy or the underlying malignancy.

Alternate dosing regimens, in which the starting dose of epoetin alfa is higher than 40,000 U once weekly, are under investigation. The hypothesized benefits of using a higher starting dose include obtaining an earlier hematologic response, a higher overall response rate (RR), and earlier identification of nonresponders. It is known that the pharmacologic response to epoetin alfa is related to dose and regimen, with greater responses observed at increasing dose levels.[15] Doses up to 1500 U/kg 3 times per week for 3-4 weeks have been administered to adults without any direct toxic effects.[16,17] Patients with myelodysplastic syndrome have safely tolerated epoetin alfa at individual doses up to 100,000 U intravenously (I.V.) twice weekly[18] and up to 1600 U/kg body weight I.V. twice weekly, although epoetin alfa is not approved for use in this population.[19] Furthermore, in pilot studies of alternate dosing regimens in anemic patients with cancer receiving chemotherapy, epoetin alfa dosed at 60,000 U once weekly for up to 16 weeks[20] or at 60,000 U once weekly followed by maintenance doses of 120,000 U every 3 weeks[21] was well tolerated and effectively increased and maintained Hb levels. These findings provided the rationale for continuing to evaluate higher starting doses of epoetin alfa in patient populations likely to benefit from earlier improvements in Hb.

The objective of the present study was to evaluate the hematologic response, safety, and clinical outcomes of epoetin alfa at a starting dose of 80,000 U once weekly in anemic patients with cancer receiving chemotherapy.

Patients and Methods

Patient Eligibility

Patients who were ≥ 18 years of age with a confirmed diagnosis of nonmyeloid malignancy, Hb ≤ 11 g/dL, Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, and who were scheduled to receive ≥ 12 weeks of chemotherapy were eligible for the study. Patients who were scheduled to receive radiation therapy during the study, had a history of thrombotic vascular events (TVEs), received a packed red blood cell (PRBC) transfusion within 28 days of study entry, or had undergone treatment with epoetin alfa or any form of erythropoietin within the previous 3 months were excluded from the study. All patients provided written informed consent.

Study Design and Treatment

This was an open-label, nonrandomized, multicenter pilot study consisting of a 12-week treatment period followed by a completion visit (week 13). The starting dose of epoetin alfa was 80,000 U once weekly administered subcutaneously. Patients received the first injection of epoetin alfa before the start of chemotherapy and then received 1 injection weekly thereafter for a maximum of 12 weeks. If a patient's Hb level increased to > 13 g/dL at any time, the epoetin alfa dose was held until Hb level decreased to ≤ 12 g/dL and was resumed at a dose of 60,000 U once weekly. The dose was also reduced if a rapid increase in Hb occurred (defined as an increase of > 1.3 g/dL in a 2-week period). To avoid depletion of iron stores and to adequately support erythropoiesis during epoetin alfa therapy, the protocol required administration of supplemental iron (ferrous sulfate 325 mg per day) to patients if it was tolerated and not contraindicated. Patients could be withdrawn for significant protocol violations or if they completed or discontinued chemotherapy.

Study Endpoints and Measurements

Hemoglobin was measured at baseline and at each weekly visit during the study (visits 1-13). Details regarding transfusions of any type received during the study were recorded at weeks 5, 9, and 13.

The primary efficacy endpoint was major hematologic response, defined as an increase in Hb ≥ 2 g/dL from baseline

or Hb ≥ 12 g/dL at any time (independent of PRBC or whole blood transfusion within the previous 28 days). Secondary efficacy measures included minor hematologic response and incidence of PRBC or whole blood transfusion. A minor hematologic response was defined as an increase in Hb ≥ 1 g/dL but < 2 g/dL (independent of PRBC or whole blood transfusion within the previous 28 days). The incidence of PRBC or whole blood transfusion was measured by the proportion of patients who received transfusions at any time during the study, from study day 1 to day 28, and after study day 28. The number of units transfused per patient was also measured.

Safety was assessed by monitoring AEs, clinical laboratory parameters, and vital signs throughout the study. Testing for serum antierythropoietin antibodies was conducted by sites that had the capability to obtain and process samples as per the central laboratory manual. Serum samples for antibody testing were taken from study patients at baseline before administration of the first dose of epoetin alfa and at the end of study (or early withdrawal). Any abnormalities in safety parameters (AEs and serious AEs) that persisted at the end of the study were followed until resolution or until a clinically stable endpoint was reached.

Statistical Methods

Efficacy analyses were performed on the modified intent-to-treat (MITT) and per-protocol (PP) populations. The MITT population included all randomized patients who received ≥ 1 dose of study drug and who had ≥ 1 postbaseline efficacy observation (Hb or transfusion). The PP population was a subset of the MITT population composed of patients who completed all study visits required by the protocol, without missing any weekly Hb measurements. Safety analyses were conducted on all patients who received ≥ 1 dose of study drug (safety population).

The primary analysis of Hb-related endpoints excluded Hb values obtained within 28 days following a PRBC or whole blood transfusion. For the MITT population, additional analyses used the last-observation-carried-forward method to impute missing and excluded Hb values. Hematologic responses were calculated as the percent of patients with a major response (increase in Hb ≥ 2 g/dL from baseline or Hb ≥ 12 g/dL) or minor response (increase in Hb ≥ 1 g/dL but < 2 g/dL from baseline) by week 5 (after 4 weeks), week 9 (after 8 weeks), and end of study. Patients were classified according to best response. Hemoglobin levels for each weekly evaluation period as well as for the change in Hb from baseline to end of study were summarized using descriptive statistics (ie, number, mean, median, and standard deviation). The proportion of patients transfused and the units of PRBCs transfused per patient were quantified using descriptive statistics, as were all safety assessments.

Table 1

Patient Demographic and Baseline Characteristics: Safety Population (N = 69)

Characteristic	Value
Mean Age ± SD, Years (Range)	61.8 ± 12.6 (32-87)
Sex, n (%)	
Male	25 (36.2)
Female	44 (63.8)
Ethnicity, n (%)	
White	61 (88.4)
Black	5 (7.3)
Hispanic	1 (1.5)
Other	2 (2.9)
ECOG Performance Status,* n (%)	
0	21 (30.4)
1	36 (52.2)
2	11 (16)
Mean Baseline Hb ± SD, g/dL (Range)	10.1 ± 0.8 (7.3-11.3)
Tumor Type†, %	
Breast	27.5
Colorectal	15.9
Ovarian	13
Non–small-cell lung	13
Other	30.4

*ECOG performance status: 0 = fully active; 1 = restricted in physically strenuous activity; 2 = ambulatory and capable of all self-care but unable to carry out work activities.
†As a result of rounding, values do not add up to 100%.
Abbreviation: SD = standard deviation

Results

Patients and Study Drug Administration

Sixty-nine patients were enrolled in the study and received ≥ 1 dose of study drug (safety population). Demographic and baseline characteristics of this population are summarized in Table 1. The mean age of patients was 61.8 years, and approximately one third (36.2%) were men. Most patients (82.6%) entered the study with an ECOG performance status of 0 or 1. Mean Hb at baseline was 10.1 g/dL. The most common tumor types were breast (27.5%), colorectal (15.9%), ovarian (13%), and non–small-cell lung (13%).

Patient disposition is summarized in Figure 1. The MITT and PP populations included 68 patients (99%) and 31 patients (45%), respectively. A total of 47 patients (68%) completed the 12-week treatment period, and 46 patients (67%) completed the

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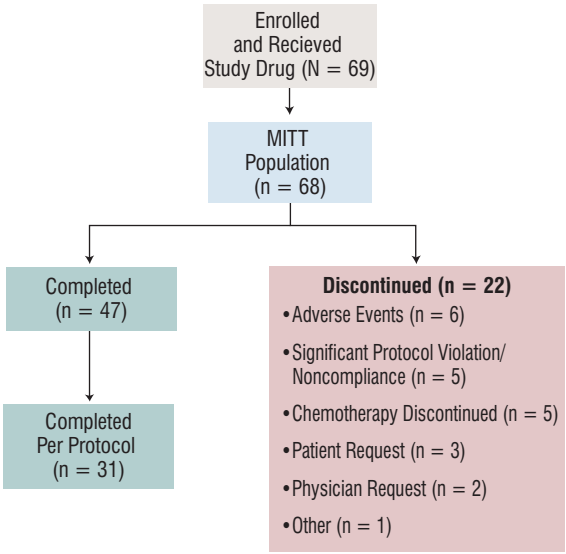
Figure 1

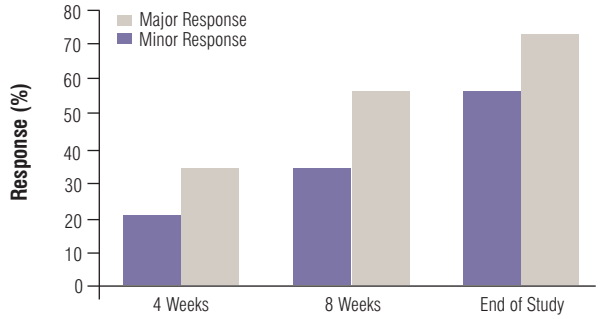
Patient Disposition



Completed per protocol is the subset of MITT population who completed all study visits required by the protocol without missing any weekly hemoglobin measurements.

Figure 2

Major and Minor Response Rates



The proportion of patients who exhibited a major response (tan bar; Hb increase ≥ 2 g/dL from baseline or Hb ≥ 12 g/dL) and the proportion of patients who exhibited at least a minor response (purple bar; Hb increase ≥ 1 g/dL but < 2 g/dL from baseline) through the first 4 weeks, 8 weeks, and the end of study (or early withdrawal). Patients are classified according to best response at each time point.

week-13 completion visit. Twenty-two patients discontinued; 6 discontinuations were caused by adverse events. Other reasons for discontinuation included significant protocol violations (missed visits) in 5 patients, discontinuation of chemotherapy in 5 patients, and patient or physician request in 5 patients.

The mean duration of exposure to study drug was 56.2 days (approximately 8 weeks). A total of 48 patients (69.6%) had ≥ 1 dose reduction or hold because of Hb > 13 g/dL, Hb increase > 1.3 g/dL in a 2-week period, or missed visits. The mean time to first dose reduction was 5.2 weeks, and the mean time to first dose hold was 7.1 weeks. By study visit 6, the mean dose received was approximately 71,300 U, and, by visit 12, the mean dose had decreased to approximately 65,800 U. The mean number of units per week, accounting for held or missed doses, was approximately 62,700 U.

Efficacy

Major responses (increase in Hb ≥ 2 g/dL from baseline or Hb ≥ 12 g/dL) and minor responses (increase in Hb ≥ 1 g/dL but < 2 g/dL) through the first 4 weeks, 8 weeks, and the end of study are summarized according to best response in Figure 2. Forty-nine patients (72%) in the MITT population exhibited a major response by the end of the study, and 13 patients (19%) achieved a minor response at best. Within the first 4 weeks of the study, 14 patients (21%) had exhibited a minor response, and 23 patients (34%) had achieved a major response. Within the first 8 weeks, 38 patients (56%) achieved a major response. The mean time to first major response was 6.7 weeks. Similar results were seen in the PP population.

Mean Hb levels increased steadily over the 12-week treatment phase from 10.1 g/dL at baseline to 12.3 g/dL at final assessment (Figure 3). The mean changes in Hb from baseline after 4, 8, and 12 weeks of therapy were 1.2, 1.9, and 2.2 g/dL, respectively. Similar results for mean Hb levels were seen in the PP population and in the last-observation-carried-forward analysis for the MITT population.

Two of 68 patients (3%) in the MITT population had received a PRBC transfusion within 3 months before study enrollment. Over the course of the study, a total of 6 patients (9%) received ≥ 1 PRBC transfusion: 4 (6%) between days 1 and 28 (mean number of units per transfusion, 2.2 units) and 2 (3%) after day 28 (mean number of units per transfusion, 2 units).

Safety

A total of 65 patients (94%) in the safety population had ≥ 1 AE; however, only 3 AEs (4%; peripheral edema, bone pain, and pruritus) were considered possibly related to study drug by the investigator. A summary of AEs that occurred in ≥ 5% of the safety population is presented in Table 2. Nausea, experienced by 15 patients (22%), was the most frequently reported AE, followed by neutropenia (19%) and constipation (17%). The majority of AEs were classified as mild or moderate, although a total of 19 patients (28%) had ≥ 1 serious AE during the study. Sepsis, reported in 3 patients 4 (%), was the most common serious AE. No serious AEs were considered by the investigator to be related to study drug. Six patients had AEs that led to discontinuation from the study, 4 of whom died within 15 days of the last dose of study drug. One additional patient died during the 30-day follow-up period. No deaths were considered by the

Table 2

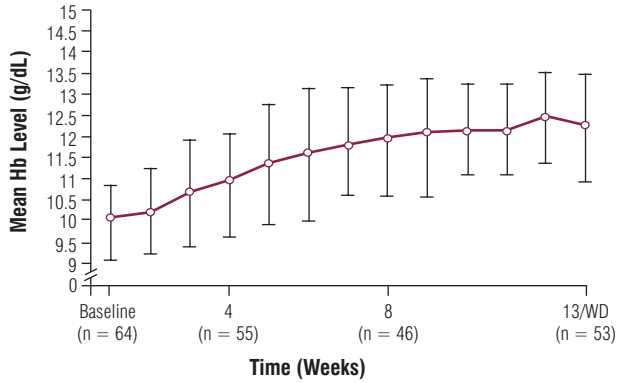
Adverse Events Occurring in ≥ 5% of Patients: Safety Population (N = 69)

Adverse Event (Preferred Term)	Number of Patients (%)
Nausea	15 (21.7)
Neutropenia	13 (18.8)
Constipation	12 (17.4)
Diarrhea	11 (15.9)
Fatigue	10 (14.5)
Edema (Peripheral)	10 (14.5)
Thrombocytopenia	8 (11.6)
Vomiting	8 (11.6)
Cough	7 (10.1)
Dyspnea (Exertional)*	7 (10.1)
Arthralgia	7 (10.1)
Dizziness	7 (10.1)
Weight Decrease	7 (10.1)
Anxiety	6 (8.7)
Dyspnea	6 (8.7)
Pyrexia	6 (8.7)
Appetite Decreased	5 (7.2)
Asthenia	5 (7.2)
Back Pain	5 (7.2)
Dehydration	5 (7.2)
Headache	5 (7.2)
Hypotension	5 (7.2)
Malaise	5 (7.2)
Palmar-Plantar Erythrodysesthesia Syndrome	5 (7.2)
Paresthesia	5 (7.2)
Upper Respiratory Tract Infection	5 (7.2)
Stomatitis	5 (7.2)
Dyspnea (Exacerbated)†	4 (5.8)
Abdominal Pain	4 (5.8)
Pain in Extremity	4 (5.8)
Pancytopenia	4 (5.8)
Sepsis	4 (5.8)
Urinary Tract Infection	4 (5.8)

*Dyspnea on exertion, increased dyspnea on exertion, shortness of breath with activity.
†Increase in shortness of breath, worsening of shortness of breath.

Figure 3

Mean Hemoglobin Levels by Study Week of the Modified Intent-to-Treat Population



Abbreviation: WD = withdrawal

investigator to be related to the study drug.

Ten patients (14.5%) in the safety population experienced a total of 11 clinically relevant TVEs. These events included deep vein thromboses (n = 3); chest wall pain (n = 3); pulmonary emboli (n = 2); and chest discomfort, chest pain, and cardiac arrest (n = 1 each). The Hb level nearest the event in all cases was ≤ 12.2 g/dL. No TVEs were considered by the investigator to be related to study drug.

No serum erythropoietin antibodies were detected during the study in 35 samples from 18 patients, and few changes in ECOG performance status from baseline to end of study were noted.

Discussion

Results from this pilot study suggest that epoetin alfa at a starting dose of 80,000 U once weekly (with subsequent dose reductions depending on Hb response) is safe and effective in treating anemia in patients with cancer receiving chemotherapy. However, the mean increases in Hb observed after 4 weeks (1.2 g/dL) and 8 weeks (1.9 g/dL) of treatment were not substantially improved over the Hb increases reported in previous studies of epoetin alfa administered at currently approved starting doses of 150 U/kg 3 times per week with dose escalation to 300 U/kg or 40,000 U once weekly with dose escalation to 60,000 U.[6-9,22,23] Furthermore, the proportion of patients (72%) who had a major response (defined as an increase in Hb ≥ 2 g/dL or attainment of Hb ≥ 12 g/dL by end of study) was only at the high end of the range of similarly defined RR (53%-70%) observed in studies of epoetin alfa at approved doses (with dose escalation for nonresponders).[8,9,21,22]

By contrast, in a small pilot study of epoetin alfa at a starting

dose of 60,000 U once weekly to increase Hb levels by ≥ 2 g/dL followed by maintenance doses of 120,000 U every 3 weeks in 20 anemic patients with cancer receiving chemotherapy, an increase in mean Hb of 2.9 g/dL and a hematopoietic RR (Hb levels ≥ 12 g/dL or Hb increase ≥ 2 g/dL) of 86% by week 8 of study were reported for weekly epoetin alfa 60,000-U dosing.[21] Moreover, Hb levels were maintained or increased with every-3-week 120,000-U dosing. A greater increase in mean Hb and a higher RR might have been observed in the present study if there had been fewer dose holds and dose reductions. Indeed, a majority of patients (70%) experienced a dose reduction or hold at some point during the study, which was reflected in the average dose per week of approximately 63,000 U. Some patients responded robustly to epoetin alfa and, as a result, had several doses held sequentially near the end of study. This may have contributed to a mean duration of exposure for the present study (approximately 8 weeks) that was substantially shorter than the maximum of 12 weeks allowed by protocol.

An important benefit of treatment with epoetin alfa is a reduction in the need for allogeneic blood transfusion. The incidence of transfusion after day 28 in the present study (3%) was lower than previously reported in the literature for epoetin alfa 40,000 U once weekly or 10,000 U 3 times per week (range, 15%-25%) in patients with chemotherapy-induced anemia and mean baseline Hb of 9.4-9.9 g/dL.[6,22] Thus, although RR and Hb increases over time were not substantially improved with 80,000 U once weekly, the results suggest that the use of higher starting doses (in combination with a mean baseline Hb of approximately 10 g/dL) may further reduce the need for transfusions compared with standard dosing in this patient population. Interestingly, the transfusion rate of 10% in a study by Patton et al,[21] which used an initiation dose of 60,000 U, was also lower than the transfusion rates observed for 40,000 U once weekly and 10,000 U 3 times per week in the previously cited studies.[6,22]

Epoetin alfa at a starting dose of 80,000 U was generally well tolerated in the present study population. Of note, the proportion of patients with clinically relevant TVEs (14.5%) in this small pilot study was slightly higher than rates observed in previous controlled studies that included 40,000 U once-weekly epoetin alfa for the correction or prevention of anemia.[6,24-26] Thrombotic vascular events have been described in patients who have chronic renal failure, have cancer and are receiving chemotherapy, or have undergone surgical procedures and are treated with epoetin alfa to Hb levels that are higher than that specified in product labeling. More recently, published results from 2 clinical trials, in which patients were given treatment to Hb levels > 12 g/dL, have suggested inferior treatment outcomes and poorer survival for the epoetin alfa and epoetin beta arms compared with placebo.[27,28] The package insert for epoetin alfa presently recommends a target Hb level of 12 g/dL and dose adjustments when the rate of Hb increase exceeds 1 g/dL in a 2-week period.[16] The epoetin alfa dose regimen used in this pilot study is higher than that currently approved.

The results of the present pilot study must be interpreted cautiously because of the small sample size and limitations inherent to the open-label, nonrandomized study design. The results of this study suggest that further exploration of alternative dosing regimens for epoetin alfa is warranted. In this regard, doses higher than the standard regimen have been shown to be generally well tolerated and effective in increasing Hb levels in our study population as well as in patients with sickle cell disease[29] and myelodysplastic syndromes.[18,30] Regimens that incorporate less frequent maintenance doses have also been explored, including dosing intervals of every 2 weeks for patients undergoing continuous ambulatory peritoneal dialysis,[31] every 2, 3, or 4 weeks in patients with predialysis chronic kidney disease,[32,33] and every 2 or 3 weeks in anemic patients with cancer receiving chemotherapy.[21,34-36]

Conclusion

Results from this pilot study suggest that epoetin alfa administered at a starting dose of 80,000 U once weekly, with appropriate dose reductions and holds, increased Hb levels in anemic patients with cancer undergoing chemotherapy; however, the RR and increases in Hb over time were not substantially improved versus previous results with approved dosing regimens. Epoetin alfa was generally well tolerated despite the use of a starting dose that exceeded recommended prescribing doses. A slightly higher proportion of patients with clinically relevant TVEs was observed in this small pilot study. Increasing Hb levels to a target of 12 g/dL in this patient population will continue to be important for combating fatigue and other anemia-related symptoms that could lead to reductions in quality of life and potentially limit the delivery of effective dose levels of chemotherapy. Further study of alternative dosing regimens in this patient population is warranted.

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