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Symptom Management and Supportive Care

Effectiveness and Safety of an Induction Therapy with Epoetin Alfa in Anemic Cancer Patients Receiving Concomitant Chemotherapy

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ABSTRACT

Background. Epoetin alfa, administered at standard dosages of 10,000-20,000 IU three times weekly or 40,000-60,000 IU once weekly, has been shown to significantly increase hemoglobin (Hb) levels, decrease transfusion requirements, and improve quality-of-life parameters in patients undergoing chemotherapy.

Objective. This open-label, nonrandomized, historically controlled study was conducted to evaluate the efficacy and safety of an induction dose of epoetin alfa in patients with moderate or severe anemia who were receiving chemotherapy.

Methods. Nineteen patients with solid tumors and Hb levels <9.0 g/dl were enrolled. The patients received single s.c. injections of epoetin alfa, 40,000 IU, on study days 1, 4, 7, 10, and 13, and were then observed for the following 30 days. Nineteen other cancer patients who had matching characteristics and had received epoetin alfa, 10,000 IU, three times weekly for the 45-day study period, served as historical controls. The primary efficacy variable was change in Hb level from baseline to days 15 (~week 2) and 45 (~week 6.5). Secondary efficacy variables included the percent response (Hb increase ≥1 g/dl) and percent major response (Hb increase ≥2 g/dl) at days 15 and 45, the durations of response and major response after day 45, the proportion of patients transfused within the 45 study days, the changes in Eastern Cooperative Oncology Group performance status score at days 15 and 45, and the ability to maintain the planned chemotherapy dose (dose intensity) over the 45-day study.

Results. Mean increases in Hb level in the epoetin alfa 40,000 IU group were significantly greater than those in the historical control group both at day 15 and at day 45. The increase in Hb level in the control group approximated increases reported with standard 3-times-weekly epoetin alfa at day 15 but was somewhat lower than the increases typically seen by day 45, presumably due to the fact that, in the present study, the epoetin alfa dose was not doubled in initial nonresponders, as is commonly done with standard epoetin alfa treatment. The rates of major response for epoetin alfa 40,000 IU patients (37% at day 15 and 84% at day 45) were higher than those for control patients (16% and 21%, respectively). Also, the transfusion rate was lower and performance status scores were better in the epoetin alfa 40,000 IU patients than in the control patients. In all, 74% of epoetin alfa 40,000 IU patients versus 47% of control patients received 100% of the planned chemotherapy dose. Epoetin alfa was well tolerated in both treatment groups.

Conclusions. Results of this study suggest that epoetin alfa at a dose of 40,000 IU administered five times over 2 weeks may confer even higher response rates than those seen with standard dosing regimens. These encouraging results support further study of the proposed induction dose of epoetin alfa in a larger, randomized, prospectively controlled trial. *The Oncologist* 2004;9:459-468

INTRODUCTION

The etiology of cancer-related anemia is multifactorial. Contributing factors may be either intrinsic (anemia of chronic disease, bone marrow involvement, blood loss, nutritional deficiencies) or extrinsic (chemotherapy or radiotherapy) [1-4]. Often, cancer-related anemia manifests symptomatically as fatigue, exhaustion, weakness, headache, respiratory distress, cardiac decompensation, or chest pain, any of which can lead to reduced adherence to therapeutic regimens, as well as diminished physical capacity and quality of life (QOL) [1, 5, 6]. Moreover, recent evidence suggests that cancer-related anemia can negatively influence therapeutic and clinical outcomes. A review of 60 papers that reported the survival of cancer patients according to hemoglobin (Hb) level or the presence of anemia showed that anemia was a strong prognostic factor for poorer survival in patients with a variety of malignancies [7]. In all studies, the median survival time was longer for nonanemic patients than for anemic patients. In the overall analysis, anemia was associated with an estimated 65% greater risk of death, ranging from 75% in patients with head and neck carcinoma to 67% in those with lymphoma, 47% in those with prostate carcinoma, and 19% in those with lung carcinoma [7]. On the other hand, higher Hb levels have been associated with better outcomes. The results of several studies in patients with cervical or head and neck cancer undergoing radiotherapy or radiochemotherapy have shown nonanemic patients to have advantages over anemic patients with respect to overall survival, disease-free survival, and local control [8-11]. In one study, patients with Hb levels ≥14.5 g/dl before radiotherapy had significantly ($p < 0.05$) higher complete response, locoregional control, and survival rates than patients with pretreatment Hb levels <14.5 g/dl whose anemia remained untreated throughout radiation therapy [10]. In another study, patients with average weekly nadir Hb (AWNH) levels ≥12.0 g/dl during radiation therapy had significantly higher 5-year survival rates and significantly lower rates of relapse, local recurrence, and distant metastases than patients with AWNH levels <12.0 g/dl, regardless of pretreatment Hb level [11].

Hb level at the start of chemotherapy has also been shown to be a strong predictor of transfusion need. Results of a large-scale United Kingdom audit ($n = 2,719$) indicated that patients with Hb levels <10 g/dl before starting chemotherapy had a significantly ($p \leq 0.03$) greater risk for receiving a red blood cell transfusion during treatment than did patients with pretreatment Hb levels >10 g/dl [12]. Unfortunately, although red blood cell transfusion is a widely used procedure, it is also associated with a number of risks, including immune suppression and iron overload, as well as possible transmission of infectious diseases such as hepatitis and HIV,

and more recently, new-variant Creutzfeldt-Jakob disease and West Nile virus. Thus, there is a need for an alternative treatment that will effectively and safely ameliorate anemia in oncology patients.

Recombinant human erythropoietin (rHuEpo, epoetin alfa) has been shown in several placebo-controlled clinical trials and single-arm, community-based studies to increase Hb levels, decrease transfusion needs, and improve QOL in anemic cancer patients undergoing chemotherapy when administered at dosages of either 10,000-20,000 IU three times weekly or 40,000-60,000 IU once weekly [13-16]. The mean increase in Hb level was approximately 1 g/dl after 4 weeks and 2 g/dl after 8 weeks of epoetin alfa therapy, irrespective of the dosage regimen used. Mean response rates in these studies ranged from 53%-70.5%, with response defined as an increase in Hb level ≥2 g/dl or achievement of an Hb level ≥12 g/dl without transfusion in the previous 30 days. In one double-blind, placebo-controlled study, the response rate was higher when treatment was started earlier, that is, when Hb levels were at or above 10.5 g/dl (80.5% versus 68.5% for patients with pretreatment Hb levels <10.5 g/dl) [17].

In an effort to explore the potential for even better response rates with respect to rapidity and duration of response in anemic cancer patients, a new epoetin alfa regimen using a 2-week induction dose was evaluated. This report describes the results of a pilot study we conducted to examine the efficacy and safety of this new dosing regimen in a subset of cancer patients with moderate-to-severe anemia who were receiving chemotherapy.

MATERIALS AND METHODS

Patients and Study Design

This was a 45-day, single-center, prospective, open-label, nonrandomized, historically controlled study with an experimental cohort of 19 patients and a retrospective control group comprising the 19 most recently treated cancer patients from our institution whose inclusion and exclusion criteria matched those of the investigational group. Patients enrolled in the study ($n = 38$) were required to be at least 18 years of age and to have a confirmed diagnosis of solid malignancy, for which they were receiving platinum or nonplatinum chemotherapy (minimum cycle duration, 3 weeks). Also, they had to have a life expectancy of 6 months or greater and Hb levels <9 g/dl. Patients with acute leukemia or myeloid malignancies, uncontrolled hypertension, or Eastern Cooperative Oncology Group (ECOG) performance status score ≥3 were excluded, as were those with an uncontrolled iron, folate, or vitamin B_{12} deficiency. Patients who had undergone ablative chemotherapy or had had an acute major infection within 1 month, allogeneic blood transfusion within 14 days, or severe illness or surgery

within 7 days of study entry, also were excluded. Patients previously treated with epoetin alfa at doses of 10,000 IU 3 times weekly (tiw) could be enrolled, provided their Hb levels had not increased by ≥1 g/dl with such treatment. All patients provided written informed consent to participate in the study.

Treatment

Prospectively enrolled consecutive patients received single s.c. injections of 40,000 IU epoetin alfa on study days 1, 4, 7, 10, and 13 (a total of five injections) and were then observed for the next 30 days (outside the U.S., epoetin alfa is manufactured by Ortho Biologics, LLC [Manati, Puerto Rico] and distributed and marketed as Eprex® or Erypo® by Ortho Biotech [Bridgewater, NJ] and Janssen-Cilag [Neuss, Germany]. In the U.S., Procrit® [epoetin alfa] is manufactured by Amgen Inc. [Thousand Oaks, CA] and distributed and marketed by Ortho Biotech Products, L.P.). To avoid restriction of erythropoiesis due to inadequate iron stores or availability, patients in the experimental arm received a single i.v. dose of 125 mg elemental iron at the beginning of the treatment period. If transferrin saturation fell to ≤20% during the treatment period, an oral daily dose of 200 mg elementary iron was administered. The historical control group had received 10,000 IU of epoetin alfa s.c. tiw for the 45-day study period. The control group had also received elemental iron supplementation orally if transferrin saturation fell to <20%, but they were not given an i.v. injection at day 1.

Efficacy and Safety Evaluations

The primary efficacy variables were the changes in Hb level from baseline to days 15 and 45. Secondary efficacy variables included percent response (Hb increase ≥1 g/dl) and percent major response (Hb increase ≥2 g/dl) at days 15 and 45, durations of response and major response after day 45, proportion of patients given blood transfusions between days 1 and 45, changes in ECOG performance status score at days 15 and 45, and ability to maintain the planned chemotherapy dose (dose intensity) over the 45 study days. Safety was evaluated mainly by monitoring adverse events.

Statistical Analyses

Means and standard deviations (SDs) of continuous variables and frequencies and proportions of discrete variables are reported. Median durations of response and major response were estimated by Kaplan-Meier analysis. Kendall's rank-correlation coefficient (τ) was used to assess the relationship between change in Hb level and ECOG performance status score. Changes in Hb level from baseline between the epoetin alfa dose groups were compared using the Student's t-test (2-sided), and 2-sided confidence intervals with 1-α = 95% (CI95) were calculated. Multivariate analyses were performed using the SAS GLM procedure to investigate the effects of patient characteristics on change in Hb level and to provide a measure of treatment effect adjusted for these factors. A $p < 0.05$ was considered significant. Fisher's exact test was used to compare response rates. ECOG performance status scores were compared by means of the Cochran-Mantel-Haenszel test controlling for baseline values.

RESULTS

The study included 38 patients, 19 of whom had been enrolled prospectively (epoetin alfa 40,000 IU group) and 19 of whom had been selected from our most recent cases to serve as historical controls (epoetin alfa 10,000 IU group). Demographic and clinical characteristics were generally similar in the two groups (Table 1). Importantly, there was no difference between the groups with respect to mean Hb level at baseline (8.34 g/dl in the epoetin alfa 40,000 IU group and 8.35 g/dl in the control group). All but one patient who entered the study had advanced (stage III or stage IV) disease, and 92% had begun chemotherapy within 3 months prior to study entry. The antineoplastic agents most commonly administered during the study are shown for each treatment group in Table 2. Overall, the distribution of chemotherapy regimens within each specific malignancy type was generally balanced between the two groups.

For all characteristics considered as covariates in the multivariate analyses, that is, age, sex, baseline ECOG performance status score, baseline Hb level, type of tumor (lung, breast, other), stage of tumor (2-3 or 4), chemotherapy line (1 or 2-3), and chemotherapy type (platinum-based or non-platinum-based), differences between the two groups were associated at $p > 0.30$.

Hematopoietic Response

Change in Hb Level

Mean changes in Hb level from baseline differed significantly between the epoetin alfa 40,000 IU group and the control group at both day 15 (1.7 ± 1.3 g/dl versus 0.4 ± 1.3 g/dl, respectively; $p = 0.0042$) and day 45 (2.9 ± 1.3 g/dl versus 0.8 ± 1.3 g/dl, respectively; $p = 0.0001$). Mean Hb levels for the two treatment groups at baseline, day 15, and day 45 (final evaluation) are shown in Figure 1. Multivariate analyses detected no significant differences ($p > 0.15$) in Hb increase at either day 15 or day 45 based on age, sex, baseline ECOG performance status score, baseline Hb level, type or stage of tumor, chemotherapy history (first-, second-, or third-line), or treatment with platinum-based chemotherapy in either group. The differences between the epoetin alfa 40,000 IU and

Table 1. Baseline demographic and clinical characteristics

Characteristic	Epoetin alfa 40,000 IU (*n* = 19)	Epoetin alfa 10,000 IU (*n* = 19)
Age (years)		
Mean ± SD	59 ± 14	61 ± 12
Range	33-78	28-80
Sex, *n* (%)		
Male	7 (37)	11 (58)
Female	12 (63)	8 (42)
Hemoglobin level (g/dl)		
Mean ± SD	8.34 ± 0.61	8.35 ± 0.45
Range	6.9-9.0	7.3-8.9
ECOG score, *n* (%)		
0	5 (26)	3 (16)
1	10 (53)	14 (74)
2	4 (21)	2 (11)
Primary site of tumor, *n* (%)		
Lung	6 (32)[a]	8 (42)
Pleura	1 (5)	0
Mediastinum	1 (5)	0
Head/neck	1 (5)	1 (5)
Breast	5 (26)	3 (16)
Ovary	1 (5)	2 (11)
Endometrium	1 (5)	0
Ureter	0	1 (5)
Colon/rectum	3 (16)	1 (5)
Pancreas	0	1 (5)
Unknown	0	2 (11)
Tumor stage, *n* (%)		
II	1 (5)	0
III	5 (26)	6 (32)
IV	13 (68)	13 (68)
Previous epoetin alfa (10,000 IU tiw), *n* (%)	11 (58)	NA
Surgery[b] within last 30 days, *n* (%)	2 (11)	0
Transfusion within last 30 days, *n* (%)	0	1 (5)
Chemotherapy history, *n* (%)		
First line	13 (68)	9 (47)
Second line	5 (26)	7 (37)
Third line	1 (5)	3 (16)
Concomitant radiotherapy, *n* (%)	0	1 (5)

[a]Includes one patient with bladder tumor in addition to a lung tumor.

[b]Minor surgery without significant blood loss.

Abbreviation: NA = not applicable.

control groups were virtually unaffected by adjusting for these factors. In the epoetin alfa 40,000 IU group, 11 patients had previously received epoetin alfa at doses of 10,000 IU tiw. The mean increase in Hb level in those patients was slightly lower than in previously untreated patients, both at day 15 (1.5 ± 1.3 g/dl versus 2.0 ± 1.2 g/dl, *p* = 0.42) and at day 45 (2.8 ± 1.6 g/dl versus 3.0 ± 0.9 g/dl, *p* = 0.76).

Response

 As additional measures of efficacy, the proportions of patients who achieved responses (Hb increase ≥1 g/dl) or major responses (Hb increase ≥2 g/dl) were determined (Fig. 2). In the epoetin alfa 40,000 IU group, the rates of response at days 15 and 45 were 74% and 95%, respectively, and the rates of major response were 37% and 84%, respectively. In contrast, response rates in the control group at days 15 and 45 were 26% and 42%, respectively, with 16% and 21% of patients achieving major responses at the respective evaluations. For those patients in the epoetin alfa 40,000 IU group who responded, the median durations of response and major response were 98 days and 71 days, respectively.

| Table 2. Most commonly used[a] antineoplastic agents		
Antineoplastic agent	Epoetin alfa 40,000 IU ($n = 19$)	Epoetin alfa 10,000 IU ($n = 19$)
Platinum compounds, n (%)	8 (42)	11 (58)
Cisplatin	5 (26)	5 (26)
Carboplatin	2 (11)	6 (32)
Oxaliplatin	1 (5)	0
Pyrimidine analogues, n (%)	4 (21)	9 (47)
Gemcitabine	2 (11)	5 (26)
Fluorouracil	1 (5)	4 (21)
Tegafur	1 (5)	0
Taxanes, n (%)	8 (42)	4 (21)
Docetaxel	5 (26)	2 (11)
Paclitaxel	3 (16)	2 (11)
Anthracyclines, n (%)	7 (37)	3 (16)
Epirubicin	5 (26)	3 (16)
Doxorubicin	1 (5)	0
Mitoxantrone	1 (5)	0
Epipodophyllotoxins, n (%)	2 (11)	4 (21)
Etoposide	2 (11)	4 (21)
Nitrogen mustards, n (%)	3 (16)	2 (11)
Cyclophosphamide	3 (16)	1 (5)
Ifosfamide	0	1 (5)
Camptothecans, n (%)	1 (5)	2 (11)
Topotecan	1 (5)	1 (5)
Irinotecan	0	1 (5)
Folate analogues, n (%)	1 (5)	2 (11)
Methotrexate	0	2 (11)
Raltitrexed	1 (5)	0

[a]>5% in either group.
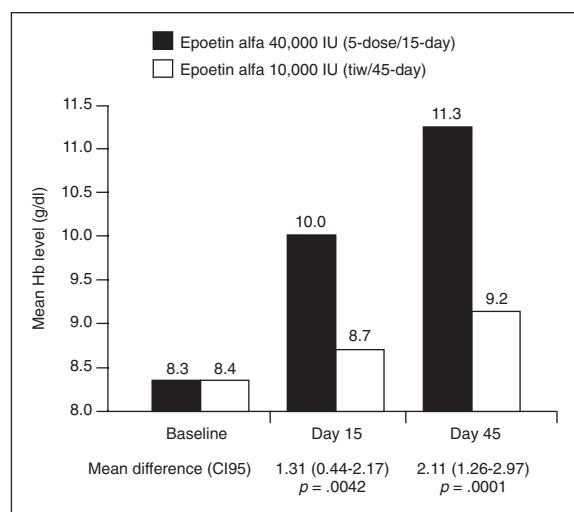
Figure 1. Mean Hb levels at baseline, day 15, and day 45 by treatment group.

Transfusion Requirements

Only one patient in the control group and no patients in the epoetin alfa 40,000 IU group had received a blood transfusion during the 30 days prior to study entry. During the 45-day study, four patients received transfusions, one (5%) in the epoetin alfa 40,000 IU group (on day 31) and three (16%) in the control group (on days 38, 39, and 44).

ECOG Performance Status Scores

Proportionally more patients in the epoetin alfa 40,000 IU group than in the control group showed improvements in ECOG performance status scores from baseline at both day 15 and day 45 (Table 3 and Fig. 3). However, the difference in the distributions of patients who had improved, were unchanged, or had worsened at these evaluations significantly favored the epoetin alfa 40,000 IU group only at day 15 (Table 3). The relationship between Hb change and ECOG performance status score was assessed by correlation analysis. Results of this analysis indicate that there was a significant correlation between improvement in ECOG performance score and a concomitant increase in Hb level from baseline at both day 15 ($\tau = –0.465$, $p = 0.0006$) and day 45 ($\tau = –0.289$, $p = 0.026$) (Table 4).
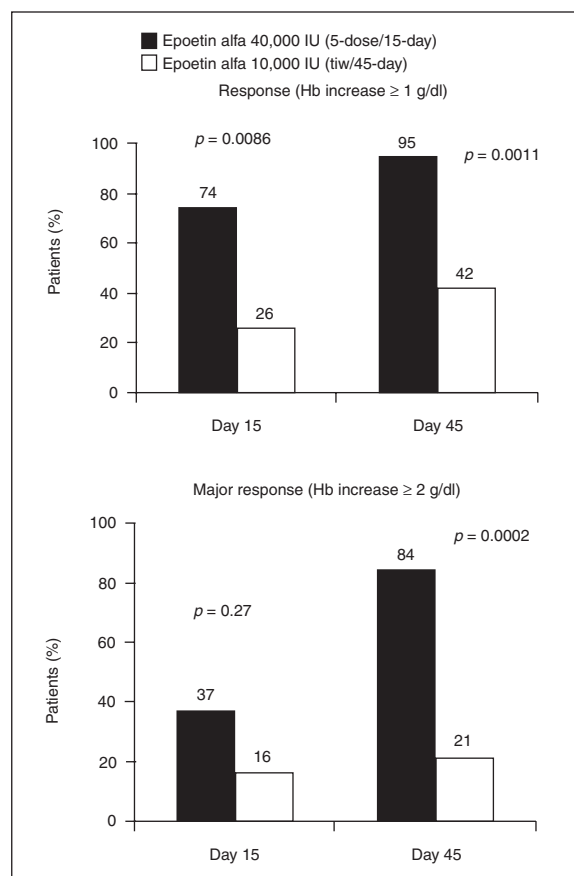
Figure 2. Mean percentages of patients with responses and major responses at day 15 and day 45 by treatment group.

Dose Intensity

The dose intensity of chemotherapy (i.e., the ratio between the dose actually administered during the study and the planned dose) was higher in the epoetin alfa 40,000 IU group, with 74% of patients in that group receiving 100% of planned chemotherapy, compared with 47% of patients in the historical control group (Fig. 4).

Safety

Epoetin alfa was generally well tolerated in the epoetin alfa 40,000 IU group. Three patients (16%) in that group experienced mild desquamative dermatitis, which was judged by the investigator as possibly related to study treatment. No change in epoetin alfa therapy was necessary, and the events regressed spontaneously after 2-5 days. Another patient in the epoetin alfa 40,000 IU group had moderate deep-vein thrombosis; however, this event was considered as unlikely to be related to the study drug because of high independent related risk factors in the patient. Again, epoetin alfa therapy was unchanged, and resolution occurred after 2 weeks of nadroparin (Fraxiparine®; Sanofi-Synthelabo; Paris, France) treatment. No patient in the control group experienced an adverse event.

DISCUSSION

During the last decade, the results of four major studies demonstrated the efficacy of standard doses of epoetin alfa (either 10,000-20,000 IU [150-300 IU/kg] tiw or 40,000-60,000 IU once weekly) in correcting anemia in cancer patients undergoing chemotherapy [14-16, 18]. Increases in Hb levels, reductions in transfusion requirements, and improvements in patients' QOL were observed in all four studies, and the changes were statistically significant across the studies. The mean increase in Hb level was approximately 1 g/dl after 4 weeks and approximately 2 g/dl after 8 weeks of epoetin alfa therapy, irrespective of the dosage regimen used. Mean response rates in those studies ranged from 53%-70.5%, with response defined as an increase in Hb level ≥ 2 g/dl or achievement of an Hb level ≥ 12 g/dl without transfusion in the previous 30 days. In the one double-blind, placebo-controlled study in this series, anemia was corrected somewhat more rapidly in epoetin-alfa-treated patients with baseline Hb levels >10.5 g/dl than in patients with baseline Hb levels below this value (i.e.,

Table 3. Change in ECOG performance status score from baseline to day 15 and day 45 by treatment group

Change from baseline	Epoetin alfa 40,000 IU ($n = 19$)	Epoetin alfa 10,000 IU ($n = 19$)
Day 15, n (%)		
Improved	12 (63)	6 (32)
Unchanged	7 (37)	12 (63)
Worsened	0	1 (5)
	$p = 0.015^a$	
Day 45, n (%)		
Improved	11 (58)	7 (37)
Unchanged	7 (37)	9 (47)
Worsened	1 (5)	3 (16)
	$p = 0.10^a$	

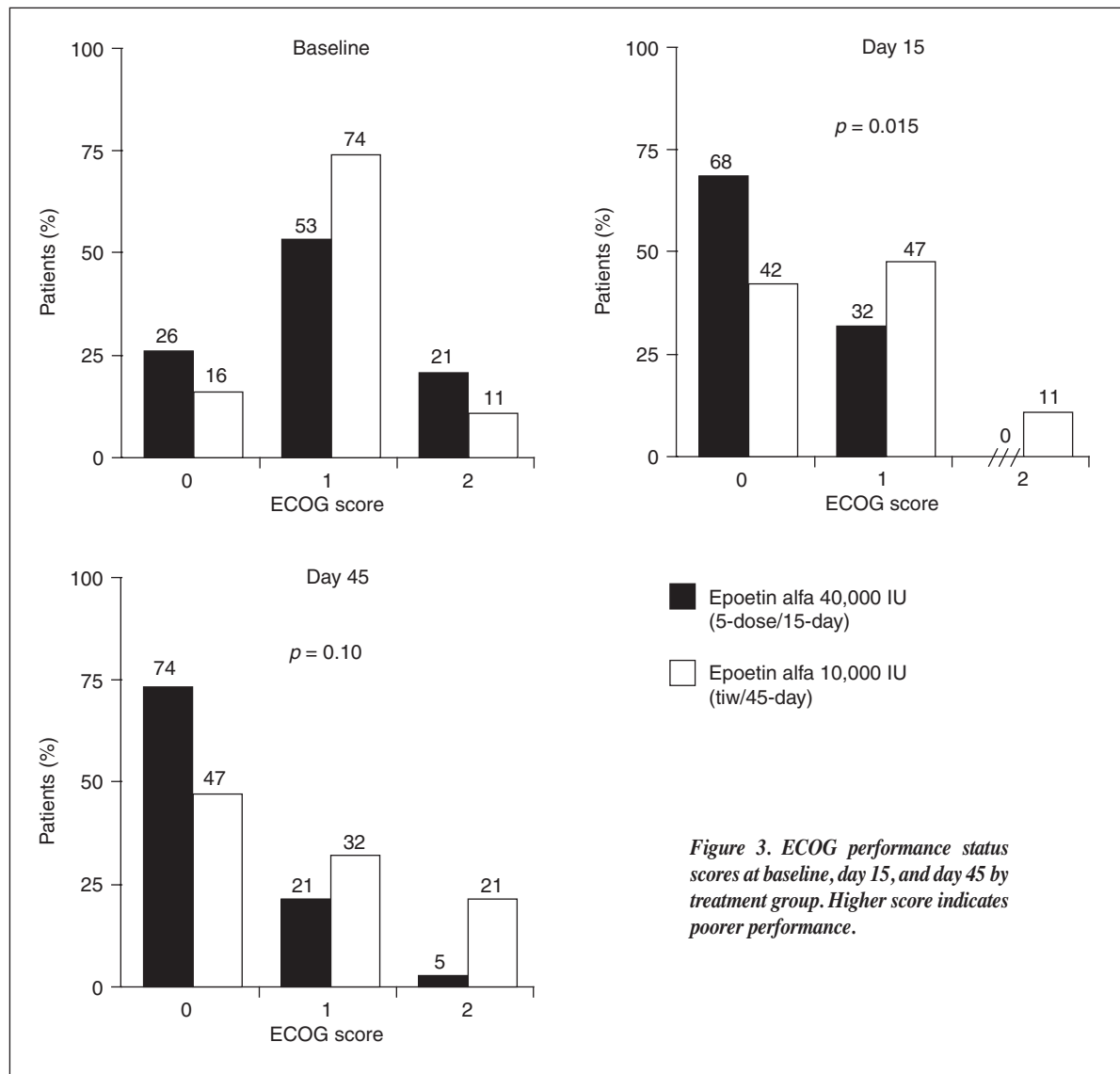[a]Cochran-Mantel-Haenszel test controlling for baseline values.

Figure 3. ECOG performance status scores at baseline, day 15, and day 45 by treatment group. Higher score indicates poorer performance.

patients in the >10.5 g/dl stratum achieved the target level of ≥12.0 g/dl after week 4, whereas patients in the ≤l0.5 g/dl stratum achieved this level after week 12). Also, the peak Hb level achieved with epoetin alfa therapy was higher for patients in the >l0.5 g/dl stratum (13.8 g/dl) than for those in the ≤10.5 g/dl stratum (12.7 g/dl) [17].

Table 4. Correlation between change in ECOG performance status score and change in Hb level ($n = 38$)

		Change from baseline	
Evaluation	n	ECOG performance status score	Mean ± SD Hb level (g/dl)
Day 15	18	−1 (improved)	+1.8 ± 1.2
	19	0 (unchanged)	+0.5 ± 1.1
	1	+1 (worsened)	−2.7
		Kendall's τ = −0.465; $p = 0.0006$	
Day 45	2	−2 (improved)	+4.6 ± 2.6
	16	−1 (improved)	+2.1 ± 1.3
	16	0 (unchanged)	+1.7 ± 1.4
	4	+1 (worsened)	+0.1 ± 2.2
		Kendall's τ = −0.289; $p = 0.026$	
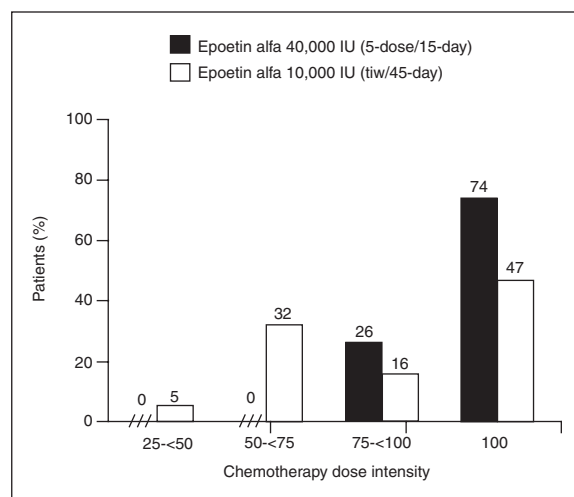
Figure 4. Dose intensity over the study by treatment group.

Overall, the findings of the four major studies suggest that standard once-weekly or tiw epoetin alfa is effective for establishing and maintaining physiological levels of Hb when the aim of treatment is to improve clinical outcome, prevent or ameliorate anemia secondary to aggressive chemotherapy, or improve QOL and avoid the incapacitating symptoms of anemia, most notably fatigue. It should be noted, however, that the mean Hb levels at the start of treatment in these studies ranged from 9.2 g/dl to 9.9 g/dl.

As indicated earlier, the objective of our study was to evaluate the efficacy and safety of a new epoetin alfa dose and schedule in cancer patients with moderate or severe anemia (baseline Hb level <9.0 g/dl). The dosage regimen investigated, 40,000 IU administered five times over a 2-week interval, was selected on the basis of available pharmacokinetic/pharmacodynamic data and encouraging results from previously reported clinical trials [19-21]. In a study of healthy volunteers, a linear relationship was found between response, measured as a percentage of reticulocytes area under the time-concentration curve (AUC), and erythropoietin AUC for single doses of epoetin alfa up to 1,800 IU/kg (~120,000 IU). Beyond these doses, however, there was a saturation of response. In addition, repeated doses of epoetin alfa were found to be more effective than single doses at maintaining erythropoietin concentrations and producing reticulocytes [19]. These observations suggest that, while erythropoietin receptors on the bone marrow progenitor cells can become saturated, erythropoiesis requires the maintenance of erythropoietin levels above certain effective concentrations, at least intermittently [20].

In the clinical setting, administration of epoetin alfa at a dose of 40,000 IU twice weekly until the achievement of a

response resulted in response rates of 54% after 4 weeks and 66% after 8 weeks in patients with low-risk myelodysplastic syndromes [22]. Encouraging results were also obtained in a very recent study in patients with advanced multiple myeloma, who had a response rate of 66% (4/6 patients) and a median increase in Hb level of 2.4 g/dl following administration of high-dose epoetin alfa (initial dose, 40,000 IU twice weekly) [23]. As those investigators indicated, the findings support further evaluation of early intervention with high-dose, short-term epoetin alfa as a strategy for managing anemia in multiple myeloma patients.

In our study, five 40,000 IU doses of epoetin alfa administered over 2 weeks quickly increased Hb levels in cancer patients with baseline Hb levels <9.0 g/dl. Importantly, the increases in Hb level over the first 15 study days (1.7 g/dl) and up to day 45 (2.9 g/dl) were significantly higher for the epoetin alfa 40,000 IU group than for the historical control group. By days 15 and 45, 74% and 95%, respectively, of patients had achieved Hb increases ≥1 g/dl, and 37% and 84%, respectively, had achieved Hb increases ≥2 g/dl. Further, the response was maintained for more than 2 months in most patients without additional treatment, even though chemotherapy was ongoing.

Worth noting is the fact that 58% of those patients were pretreated with standard regimens of epoetin alfa without achieving either a major or a minor response, while the high-dose treatment produced a response rate near to that achieved in non-previously treated patients. According to international studies [24], 125 mg of elemental i.v. iron therapy administered on day 1 in the epoetin alfa 40,000 IU group and never given to the control group, marginally affected these results (<5%). Also, performance status was better and dose intensity of chemotherapy was higher in the epoetin alfa 40,000 IU group than in the control group, suggesting that correction of severe anemia may additionally offer benefits with respect to patient QOL and treatment outcomes. The use of QOL instruments might also be informative when planning future trials.

With respect to the historical control group used in our study, it should be noted that the increases in Hb level in this group approximated those reported with standard tiw epoetin alfa therapy at day 15, but were somewhat smaller than the increases typically seen by day 45. In the placebo-controlled study cited above [16], increases in Hb level after 6 weeks (~42 days) of treatment were approximately 1.3 g/dl for patients with baseline Hb levels ≤10.5 g/dl and 1.5 g/dl for those with baseline Hb levels >10.5 g/dl. A possible explanation for the relatively small increases in Hb level in our historical control group is the fact that the epoetin alfa dose was not doubled after 4 weeks in initial nonresponders, as is recommended for standard therapy.

Overall, the findings of our study suggest that an induction dose of epoetin alfa may overcome a possible intrinsic resistance of hematopoietic progenitor cells and stimulate differentiation by increasing receptor saturation at an early stage. Such an event may mimic what happens naturally. Several papers have described the physiology of endogenous erythropoietin in response to hypoxia [25, 26]. In studies at high altitude and in closed-environment hypoxic atmospheres, rapid increases in the concentration of endogenous erythropoietin in response to hypoxia were detected within a few hours to a few days, followed by decreases to normal levels when other compensatory mechanisms had been activated. The subsequent hematocrit response was detectable by the end of the serum erythropoietin peak and increased thereafter. This finding supports the proposition that a high dose of rHuEpo is necessary for recruitment of early precursor cells, whereas a low dose is sufficient to stimulate further differentiation. Since moderate and severe anemia can cause hypoxia that cancer patients cannot overcome by the secretion of endogenous erythropoietin [27], a brief, pharmacologic induction dose of exogenous erythropoietin (rHuEpo) might mimic the natural physiologic response, and thereby further erythropoiesis, which may be of benefit in certain cancer patient populations.

In summary, the initial experience with the new epoetin alfa dosage schedule described here suggests that a higher induction dose of epoetin alfa may afford a high rate of rapid response in anemic cancer patients, including those with severe anemia and a resultant highly compromised bone marrow. These encouraging results could provide the rationale for randomized, prospectively controlled trials, where a short high-dose treatment with epoetin alfa can be compared with a control arm with a standard regimen (10,000 IU tiw or 40,000 IU weekly).

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