

## Evaluation of Epoetin Supplemented with Oral Iron in Patients with Solid Malignancies and Chronic Anemia not Receiving Anticancer Treatment

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**Abstract.** *Objective: To evaluate the effectiveness and improvement in quality of life (QOL) of epoetin alfa administration supplemented with oral iron as a therapeutic regimen for patients with solid malignancies and anemia of chronic disease (ACD), not receiving chemotherapy and/or radiotherapy. Patients and Methods: A total of 100 patients with cancer-related anemia, not subjected to chemotherapy and/or radiotherapy, were randomized to receive for a maximum of 24 weeks either oral iron, equivalent to 200 mg elemental iron once daily, or epoetin alfa 40,000 IU subcutaneously once weekly plus oral iron once daily. Results: Patients in the epoetin alfa group had, from baseline to study end, a mean increase in hemoglobin (Hb) levels of 2.4 g/dL, whereas in the control group the mean Hb level decreased by 0.1g/dL, ( $p < 0.001$ ). Improvement in QOL as assessed by the LASA and the FACT-An questionnaire were greater in patients in the epoetin alfa group than in the control group (mean change, LASA-energy level: 30.4 mm vs. 0.4 mm, -daily activities: 31.7 mm vs. 0.4 mm, -overall well-being: 32.4 mm vs. 4.9, FACT-An: 43.3 vs. 13.4, respectively). As for ECOG score, patients in the epoetin alfa group had a mean improvement of 0.16 from baseline to study end (control group: 0.06). Improvement in QOL parameters and in ECOG scores correlated positively with increased hemoglobin levels. Conclusion: Our results suggest that weekly epoetin alfa therapy supplemented with daily oral iron increases Hb levels and improves QOL in patients with solid malignancies and ACD who are not receiving chemotherapy and/or radiotherapy. This*

*regimen offers optimal therapy in this population taking into consideration physician's convenience and patient's compliance.*

Anemia is a frequent complication in cancer patients, resulting either from the disease itself or from the effects of cancer treatments, particularly chemotherapy or radiotherapy (1). The etiology of anemia in these patients is multifactorial and usually attributable to bone marrow tumor infiltration, poor nutritional status, bleeding or, more commonly, to the syndrome referred to as anemia of chronic disease (ACD) (2). ACD is characterized by mild to moderate erythroid hypoplasia of the bone marrow, a modest decrease in red cell survival and decreased bone marrow reutilization of iron, with patients exhibiting serum erythropoietin levels that are elevated above normal, but not as high as those demonstrated in patients with similar hemoglobin decreases caused by iron deficiency anemia or hemolytic anemia (3). It appears that cancer patients experience a blunted erythropoietin response to anemia, in addition to inadequate erythropoietin production (3, 4). These two factors may play an important role in the development and persistence of anemia in cancer patients (3, 5). Moreover, such anemia may negatively affect the quality of life (QOL) in cancer patients, producing symptoms such as fatigue, weakness, depression, nausea and vertigo, thus making them unable to work or fulfill their family and social activities. Effective treatment of anemia is, therefore, an important issue in the management of patients with cancer.

Data from several clinical trials have shown that recombinant human erythropoietin alfa (rHuEPO; Eprex; Janssen-Cilag), administered at a dose of 10,000 IU to 20,000 IU or 150 IU/kg to 300 IU/kg three times weekly or 40,000 IU to 60,000 IU once weekly, resulted in increased hemoglobin levels, improved QOL and decreased transfusion use in anemic cancer patients receiving chemotherapy (6-10).

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Another small number of clinical trials assessed the administration of epoetin alfa in patients with solid malignancies and ACD, not receiving chemotherapy (11, 12). Data from these studies showed that patients administered with epoetin alfa experienced significant increases in hemoglobin levels, significant improvement in their QOL and a decreased need for transfusions. Recent reports have also shown that iron supplementation results in the improvement of the Hb response to epoetin alfa, both in patients with anemia related to chronic kidney disease and in anemic cancer patients with chemotherapy-related anemia (13, 15).

This study was designed to evaluate the efficacy of epoetin alfa administration in patients with solid malignancies and ACD disease, who were not receiving chemotherapy and/or radiotherapy.

## Patients and Methods

**Patients.** Patients eligible for inclusion were  $\geq 18$  years with a confirmed diagnosis of solid malignancy and baseline hemoglobin level  $\leq 11$  g/dL. The patients should not have received or been scheduled to receive chemotherapy or radiotherapy within 3 months prior to their study enrollment until the end of the trial. All patients had a life expectancy of at least 4 months and were required to have an Eastern Cooperative Oncology Group performance status score  $\leq 2$ . Participants in this trial could not have B12 ( $< 200$  pg/mL), folic acid ( $< 2.5$  ng/mL) or iron (ferritin  $< 20$  ng/mL) deficiencies.

Patients with uncontrolled hypertension (diastolic pressure  $> 100$  mm Hg), a history of seizures within 6 months before enrollment, chronic renal insufficiency requiring hemodialysis or anemia attributable to factors other than cancer (*i.e.* chemotherapy or radiotherapy, iron, folic acid or B12 deficiencies, bleeding or hemolysis), were excluded. The study was conducted in accordance to the current revision of the Declaration of Helsinki, and local ethics committee approval was obtained before study initiation. All patients provided informed consent before enrollment.

**Study design.** This was a prospective, randomized, double-blind comparative study which enrolled a total of 100 patients. Baseline information included patient demographics, medical history and clinical examination, histology and stage of malignancy, previous chemotherapy and/or radiotherapy regimens and transfusion history. Laboratory tests performed at baseline included determination of hemoglobin, hematocrit, serum ferritin and iron levels, as well as absolute reticulocyte count and endogenous serum erythropoietin level. The data collected at baseline also included an Eastern Cooperative Oncology Group performance status score and two self-administered QOL assessments using the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire and the Linear Analog Scale Assessment (LASA) instrument. The FACT-An and LASA scales have been validated in cancer populations demonstrating sensitivity to hemoglobin (16-18) and, therefore, were considered suitable for detecting any changes in QOL due to administration of epoetin alfa and a subsequent increase in hemoglobin. The FACT-An is a questionnaire that assesses fatigue and anemia-related concerns in people with cancer.

The patients were treated and followed for a maximum of 6 months and had scheduled evaluation visits at 2-week intervals for the first 2 months and every month for the next 4 months. Clinical examination and all laboratory tests were performed at each subsequent visit from baseline. Data for transfusion requirements and adverse events were also recorded. Additionally, the patients' Eastern Cooperative Oncology Group performance status scores were obtained every month and their QOL was evaluated at the end of every month from month 2 to 6.

The enrolled patients were randomly assigned to two treatment groups: (i) human recombinant erythropoietin alfa group and (ii) control group. All patients received oral iron. Patients in the first group received epoetin alfa (Eprex) at an initial dose of 40,000 IU subcutaneously once weekly, with concomitant administration of oral iron equivalent to 200 mg elemental iron once daily. If, after the first 4 weeks of therapy, the hemoglobin level had increased by  $\geq 1$  g/dL above baseline, epoetin alfa was continued at the initial dose. However, if the hemoglobin level had increased by  $< 1$  g/dL, the dose was doubled to 40,000 IU twice weekly. If the hemoglobin level exceeded 15 g/dL at any time, epoetin alfa treatment was temporarily discontinued until the hemoglobin level decreased to less than 12 g/dL and it was then resumed to the initial dose. The dose of epoetin alfa was also reduced if hemoglobin levels increased rapidly (more than 1 g/dL over a 2-week period). Patients in the control group received a matching volume of placebo subcutaneously once weekly and oral iron.

A hematopoietic response to therapy was defined as an increase in hemoglobin of at least 2g/dL or achievement of a hemoglobin level of at least 12 g/dL without transfusion use at any time during the study. Patients who received transfusions during the study were deemed non-responders and values from their last assessment before transfusion were carried forward for the analysis of primary and secondary variables of the study. Any patient who had been treated and followed up for at least 4 months was considered to have completed the trial.

The primary efficacy variable was defined as the change in hemoglobin level in patients with solid malignancies and ACD from baseline to end-point. The secondary efficacy variables included the change in QOL scores from baseline to end-point and the proportion of patients who withdrew due to deterioration of their anemia and/or had been transfused during the trial. Safety was evaluated in the usual way by monitoring adverse events, reported by patients throughout the study either spontaneously or in response to questioning by the investigator.

**Statistical analysis.** To detect a difference of 1.2 g/dL (SD=2) in hemoglobin levels from baseline to 24 weeks, 100 patients were required to provide 80% power and a significance level of 0.05. A sample size of 100 patients would have allowed for a drop-out rate of up to 30%. All statistical analyses were conducted on the intent-to-treat population (ITT), which was defined as all randomized patients who had at least 2 time-point measurements. Analysis was performed at each evaluation visit (weeks 2, 4, 6, 8, 12, 16, 20 and 24) using the patient's last non missing post-baseline assessment (last observation carried forward, LOCF). The change from baseline to each time-point measurement for all variables was compared between groups using independent samples *t*-test or the Mann-Whitney test. All tests were two-sided with 95% significance level. Statistical analysis was performed using the statistical package SPSS v10.00 (Statistical Package for the Social Sciences).

Table I. Baseline demographic and clinical characteristics of enrolled patients.

Characteristic	Control group (n=50)	Epoetin group (n=50)
Sex		
Male	17	22
No. of patients %	34	44
Female	33	28
No. of patients %	66	56
Age, years		
Median	63.0	64.5
Range	32-79	41-79
Hb, g/dL		
Mean	10.15	9.87
SD	0.45	0.50
Hct, %		
Mean	30.99	29.98
SD	1.62	1.70
Ferritin, pmol/L		
Mean	120.96	147.96
SD	46.63	75.03
Epo, mU/mL		
Mean	171.56	100.69
SD	85.92	55.09
Fe, µg/dL		
Mean	35.33	54.47
SD	16.59	22.13
LASA, mm		
Energy		
Mean	34.1	31.8
SD	10.5	6.9
Activities		
Mean	36.2	30.7
SD	14.7	5.3
Overall well-being		
Mean	35.0	30.6
SD	12.8	7.0
FACT-An score		
Mean	66.61	67.60
SD	23.72	26.76
ECOG score		
Mean	1.86	1.90
SD	0.35	0.30

*Abbreviations:* Hb, hemoglobin; Hct, hematocrit; Epo, erythropoietin; Fe, serum iron; SD, standard deviation; LASA, Linear Analog Scale Assessment; FACT-An, Functional Assessment of Cancer Therapy-Anemia; ECOG, Eastern Cooperative Oncology Group.

## Results

A total of 100 patients were enrolled in this study and were randomly assigned to receive either oral iron plus epoetin alfa (epoetin alfa group) or oral iron only (control group) at a 1:1 ratio. The baseline demographics and clinical characteristics were comparable between the epoetin alfa and control groups (Table I). Patients enrolled in this study had various tumor types (primary or metastatic tumors): most common cancer diagnoses in the epoetin alfa group were pancreatic cancer (36%), cancer in the genital system (32%) and colon cancer (16%), whereas in the control group the most common cancer diagnoses were cancer in the genital system (22%), lung cancer (18%) and colon and pancreatic cancer (16% each). In the epoetin alfa group, 42 patients (84%) completed the study successfully, while 8 patients (16%) discontinued epoetin alfa therapy before week 24, due to inadequate response to therapy (6 patients; 12%), death (1 patient; 2%) and other reasons (*i.e.* patient's decision) (1 patient; 2%). On the other hand, in the control group 28 patients (56%) completed the study successfully and a total of 22 patients (44%) withdrew early, due to deterioration of anemia (20 patients; 40%) and death (2 patients; 4%). Despite the initial criterion of life expectancy of at least 4 months, 3 patients from both groups died before week 16. The dose of epoetin alfa was doubled to 40,000 IU twice weekly in 9 patients (18%) of the epoetin alfa group. The mean baseline hemoglobin levels were  $9.9 \pm 0.5$  g/dL for patients in the epoetin alfa group and  $10.1 \pm 0.45$  g/dL for patients in the control group. The mean baseline hematocrit levels were 30% and 31% in the epoetin alfa and the control groups, respectively, and baseline serum erythropoietin levels were  $152.7 \pm 65.1$  mU/mL and  $171.6 \pm 85.9$  mU/mL, respectively.

*Hematopoietic response.* Hemoglobin levels were determined throughout the trial. In the epoetin alfa group, patients showed a significant mean increase in hemoglobin level ( $0.3 \pm 0.2$  g/dL) from baseline to week 2 ( $p < 0.001$ ), reaching a mean increase of  $2.4 \pm 1.3$  g/dL by week 24. In the control group, the mean hemoglobin levels exhibited a marginal decrease during the study period with a mean difference of  $-0.1 \pm 1.02$  g/dL from baseline to week 24 (Figure 1). The mean change in hemoglobin level from baseline to week 24 was significantly greater in the epoetin alfa group compared to control group ( $p < 0.05$ ). In general, 38 patients (76%) in the epoetin group achieved increases in hemoglobin levels of at least 2 g/dL by week 24, compared with 0% of patients in the control group ( $p < 0.005$ ). Likewise, the mean change in hematocrit level from baseline to week 24 was statistically greater in the epoetin alfa group compared to the control group (mean changes  $7.1 \pm 3.8$  and  $-0.5 \pm 3.6$  respectively,  $p < 0.05$ ) (Figure 1). As for erythropoietin levels, in the epoetin alfa group patients demonstrated a significant mean decrease from baseline to

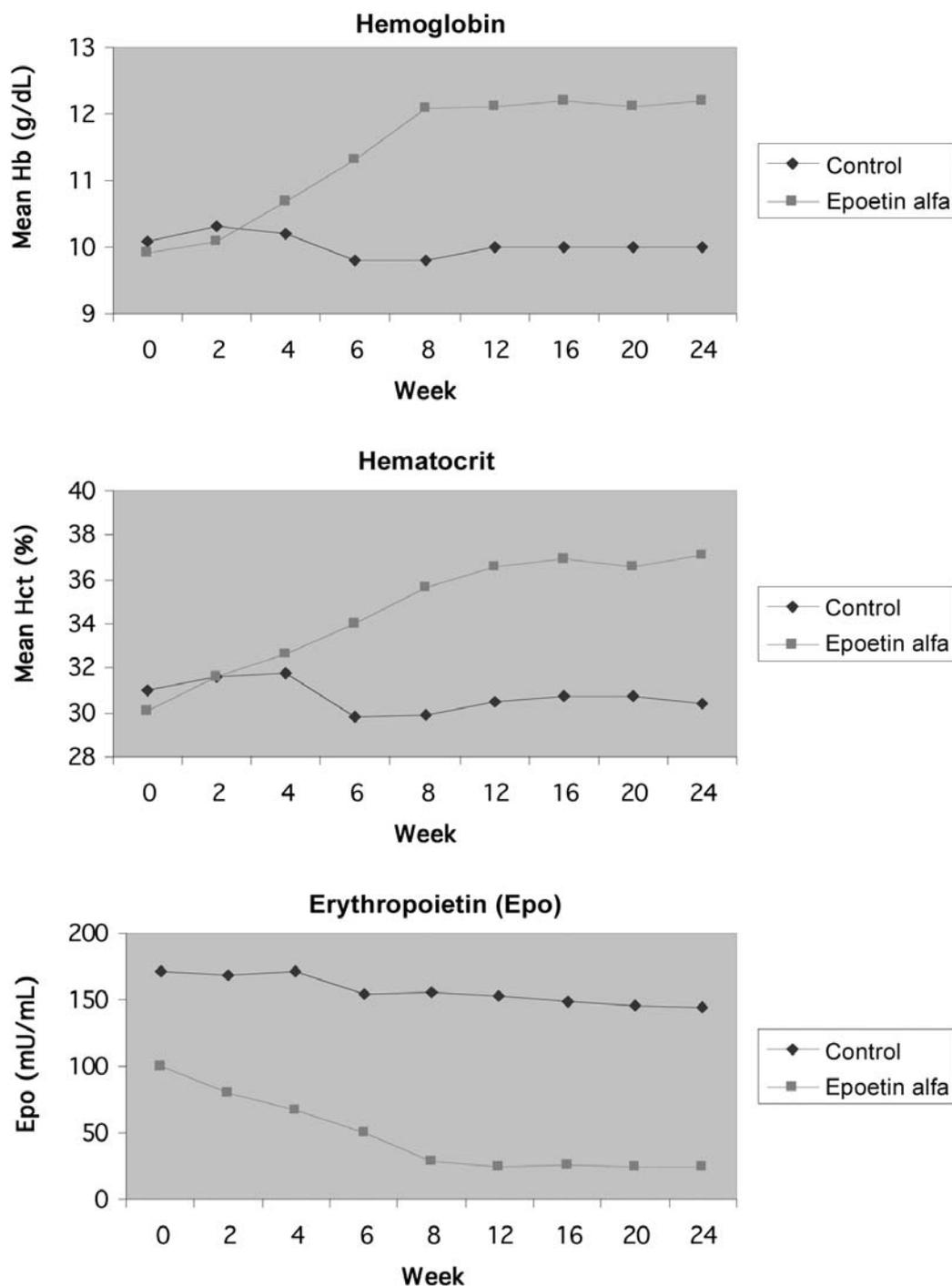


Figure 1. Mean hemoglobin, hematocrit and serum erythropoietin levels for patients in the two treatment groups from baseline to study end. Missing values at any evaluation point are replaced by last value carried forward.

week 2 ( $-21.0 \pm 18.2$  mU/mL), which continued until week 12. Thereafter, serum erythropoietin levels were generally stable with a final mean decrease of  $-76.5 \pm 53.2$  mU/mL at week 24. In the control group, the erythropoietin levels decreased

gradually reaching a mean difference of  $-27.6 \pm 46.2$  mU/mL in week 24. The mean change in erythropoietin level from baseline to week 24 was statistically greater in the epoetin alfa group compared to the control group ( $p < 0.05$ ) (Figure 1).

**QOL measures.** QOL was evaluated at the beginning of the study and at weeks 6, 16 and 24 (end of the study), using two different tools: three LASA questions and the FACT-An questionnaire. Overall, the data collected by the FACT-An questionnaire correlated well with that collected by the LASA instrument.

**LASA.** All mean baseline scores for the LASA were lower than 50 mm on the 100-mm-scale (energy level =  $31.8 \pm 7$  mm and  $34.1 \pm 10$  mm, daily activities =  $30.7 \pm 5$  mm and  $36.2 \pm 15$  mm and overall well-being =  $30.6 \pm 7$  mm and  $35.0 \pm 13$  mm, for the epoetin alfa group and control group, respectively), which suggested impairment of functioning and, therefore, substantial limitations to QOL for these patients. The mean change in energy level from baseline to study end was  $4.0 \pm 10$  mm for the control group and  $30.4 \pm 15$  mm for the epoetin alfa group. The mean change in daily activities level from baseline to study end was  $0.4 \pm 5$  mm for the control group and  $31.7 \pm 14.2$  mm for the epoetin alfa group. The mean change in overall well-being level from baseline to study end was  $4.9 \pm 13.1$  mm and  $32.4 \pm 16.1$  mm, respectively. Hence, the mean changes from baseline to study end for all three parameters of the LASA instrument were significantly higher in the epoetin alfa group ( $p < 0.0005$ ).

**FACT-An.** Evaluation of the changes in FACT-An scores for the ITT population from baseline to weeks 6, 16 and 24 demonstrated an overall improvement, as the mean change from baseline to week 24 of  $13.4 \pm 14.2$  in the control group and of  $43.3 \pm 18.4$  in the epoetin alfa group. The mean change from baseline to week 24 was statistically significantly higher in the epoetin alfa group ( $p < 0.0005$ ). As with the LASA data, the FACT-An scale revealed a marked difference between the results of the two groups, in favor of the epoetin alfa group.

**ECOG performance status scores.** The ECOG performance status was determined at baseline, at weeks 4, 8, 12, 16 and 20 and at the end of the study. At baseline, the mean score was  $1.86 \pm 0.35$  and  $1.90 \pm 0.30$  for patients in the control group and in the epoetin group, respectively. At the end of the study, the mean change in ECOG score for the remaining patients in the two groups was  $-0.06 \pm 0.2$  and  $-0.16 \pm 0.5$  in absolute values, respectively ( $p < 0.0005$ ). Therefore, changes in hemoglobin levels had a similar effect on the ECOG performance status score, as noted both with the LASA and FACT-An QOL scores.

## Discussion

Over the last decade, the results from several studies showed that epoetin alfa significantly increased hemoglobin

levels and this was associated with improved energy level, ability to perform daily activities and overall QOL (6-8,19-22). Chemotherapy, as the standard treatment for the majority of malignancies, is the principle cause of anemia in tumor-bearing individuals, while patients who do not receive chemotherapy may also have cancer-related anemia with characteristics of ACD (2). This study evaluated the effect of epoetin alfa administration in patients with solid malignancies and cancer-related anemia, who were not undergoing chemotherapy and/or radiotherapy.

During epoetin alfa administration, large amounts of iron are required to keep pace with the demands of epoetin alfa-stimulated erythropoiesis, even if the patient has adequate iron stores. Therefore, in this study, we decided to administer iron orally.

To date, few reports have evaluated epoetin alfa in cancer patients with ACD who were not receiving chemotherapy and/or radiotherapy (12, 14, 23, 24). Data from the current study revealed that the administration of epoetin alfa together with oral iron supplementation in anemic cancer patients, who were not receiving chemotherapy and/or radiotherapy, resulted in a significant increase in hemoglobin and hematocrit levels in the epoetin alfa group compared to the control group (mean change 2.4 g/dL vs.  $-0.13$  for hemoglobin, and 7.1 vs.  $-0.5$  for hematocrit,  $p < 0.05$ ). The mean endogenous serum erythropoietin levels were elevated at baseline in both groups due to ACD and in both groups decreased gradually (iron repletion always decreases EPO levels), reaching a mean difference of  $-27.6$  mU/mL in the control group and of  $-76.5$  mU/mL in the epoetin alfa group by week 24. The mean change in the epoetin alfa group was greater as an effect of the additional administration of recombinant human epoetin alfa in this group.

In addition to the efficacy of epoetin alfa plus oral iron with respect to hematopoietic parameters, the present study demonstrated a strong positive effect of this regimen on QOL measures. Results showed significant improvement ( $p < 0.0005$ ) for the epoetin alfa group over the control group from baseline to study end for all three LASA scores (energy levels, ability to do daily activities and overall well-being). Similarly, results from the FACT-An questionnaire revealed that patients in the epoetin group experienced a significant improvement in their QOL, with a mean change in the FACT-An score of 43.3 from baseline to the end of the study, whereas in the control group, the mean change in score was only 13.4. The changes observed in the LASA and FACT-An scores further confirm that improvement in QOL is associated with an increase in hemoglobin level.

The ECOG performance scores were collected throughout the study and the data showed a greater overall improvement in patients of the epoetin alfa group ( $0.16$  vs.  $0.06$  in the control group,  $p < 0.0005$ ).

Interestingly, a significantly greater percentage of patients in the control group than in the epoetin alfa group dropped out due to inadequate response to therapy and deterioration of anemia (44% of patients in control group vs. 16% in the epoetin alfa group). A total of twenty patients in the control group had hemoglobin levels  $\leq 9$  g/dL during the 24 weeks and they had to be discontinued from the study and transfused, whereas in the epoetin alfa group the respective number of patients was only 6.

In conclusion, the current study demonstrates that cancer patients with solid malignancies and ACD can benefit significantly with epoetin alfa supplemented with oral iron. A subcutaneous epoetin alfa dosage of 40,000 IU once-weekly, with supplementation of oral iron equivalent to 200 mg of elemental iron once-daily, effectively increased hemoglobin levels and improved quality of life in patients with cancer-related anemia. This regimen is convenient for both patients and physicians and can lead to improved patient compliance as well as optimal response to therapy.

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