

Bon Secours Richmond  
Pharmacy and Therapeutics Committee  
Erythropoietin  
3/2004

**Recommendations: MEC Approved MPMC/RCH/SMH**

**Chemotherapy Induced anemia**

- Epoetin 40,000 units once a week will be converted to approximately 150 units/kg three times a week or 225 units twice a week depending on patient weight (see chart below) as less total epoetin is required to achieve similar results. Randomized controlled trials utilized weight based dosing.
- The rate of rise in: Hgb, reticulocyte count, and RBCs is the same for 150 units/kg three times a week or 40,000 units once a week.
- The pharmacodynamic responses of the three times weekly and once weekly dosing regimens are similar. Although the serum erythropoietin AUC for every week dosing is larger than that of three times a week dosing the AUC (reticulocytes), AUC (Hgb) and the AUC (RBC) are comparable. Serum erythropoietin levels for every week dosing drop below three times a week dosing 4 days post injection.
- Epoetin 60,000 units once a week will be converted to approximately 225 units/kg three times a week (see chart below)
- A conservative estimate of cost saving per year by converting to protocol dosing is \$ 76,021.

**Anemia of Chronic Kidney Disease**

- Epoetin will be administered two to three times a week by the subcutaneous route. (National Kidney Foundation/DOQI Clinical Practice Guideline for Anemia of Chronic Kidney Disease: Update 2000)
- The subcutaneous route of administration will be used, as it is 30-50% more efficient than intravenous administration. The National Kidney Foundation recommends subcutaneous administration for dialysis patients and virtually all studies in oncology patients employed subcutaneous administration. Typically, a patient requires 50% more epoetin to maintain the same Hgb when epoetin is administered by the IV route as compared to the subcutaneous route.
- Epoetin doses will be rounded to the closest vial size or combination of vials that results in a injection volume of  $\leq 2$ ml. (2,000, 4000, 6,000, 8,000, 10,000, 12,000, and 14,000 units)

Dosing Conversion For 40,000 Units Once A Week	
Weight (kg)	Dose and Frequency (Approximately 450 units/kg/week for <81 kg)
36-50	10,000 units twice a week
51-55	12,000 units twice a week
56-70	10,000 units three times a week
71-80	12,000 units three times a week
$\geq 81$	20,000 units twice a week

Dosing Conversion For 60,000 Units Once A Week	
Weight (kg)	Dose and Frequency (Approximately 675 units/kg/week for < 71 kg)
36-45	10,000 three times a week
46-55	12,000 three times a week
56-70	14,000 three times a week
$\geq 71$	20,000 three times a week

**Findings:**

**Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology**

- Anemia due to malignancy may be related to either:
  - Infiltration of the marrow
  - Impaired production directly related to treatment
  - Nonspecific processes such as the inhibitory effect of tumor necrosis factor
- Epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level  $\leq 10$  gm/dl.
  - Response to epoetin is consistent across cancer types (breast, gynecologic, lung, hematologic)
- No trials reported data to evaluate whether epoetin improves symptoms or quality of life among patients with baseline hemoglobin levels of 10-12 g/dl.

- The recommended dose is 150 units/kg three times weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 units/kg three times a week for an additional 4-8 weeks in those who do not respond to the initial dose. Dosage escalation is recommended when Hgb has not achieved at least a 1 g/dl rise over baseline Hgb, and the reticulocyte is count below 40,000/ul by the 4<sup>th</sup> week of treatment. Once weekly dosage regimens are supported by less strong evidence.
- Randomized controlled trials utilized weight based dosing; no randomized trials have directly compared weight-based dosing versus uniform dosing.
  - Incidence and type of adverse events are similar for epoetin administered three times weekly and once weekly
- Continuing epoetin treatment beyond 6-8 weeks in the absence of response (eg, less than 1-2 g/dl rise in Hgb), assuming appropriate dose increase has been attempted in the nonresponder does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. Usually the Hgb increases by approximately 1 g/dl per month for the first two month (see graphics in abstract section).
- Hemoglobin levels can be raised to (or near) a concentration of 12 g/dl, at which time, the dosage of epoetin should be titrated (*reduce the dose by 25%*) to maintain that level or restarted when the level falls to near 10 g/dl. Insufficient evidence to date supports the normalization of hemoglobin to above 12 g/dl. No randomized controlled studies in cancer have been conducted to validate the additional benefit of routinely improving hemoglobin above the level of 12 g/dl. *If Hgb increases by greater than 2 g/dl in a month a dosage reduce o 25% is recommended.*
- Pharmacokinetic studies demonstrate that three times weekly and once weekly dosing regimen with higher doses of epoetin achieve similar rises in reticulocyte counts.
- Evidence for hemodialysis patients suggests that subcutaneous administration is 30-50% more efficient than intravenous route.
- Once weekly dosing strategies are more appropriate for outpatients. They were developed to decrease the number of office visits.
- Virtually all studies evaluating the effectiveness of epoetin have employed subcutaneous administration.
- Epoetin induced increase in Hgb reduces transfusion requirements and improves patient quality of life.

Metaanalysis of effect of epoetin on transfusions in chemotherapy induced anemia		
	Odds Ratio	NNT
All randomized studies (subcutaneous administration)	0.38 (0.282-0.513)	4.4 (3.6-6.1)
All high quality randomized studies (subcutaneous)	0.453 (0.33-0.621)	5.2 (3.8-8.4)
All lower quality randomized studies (subcutaneous)	0.137 (0.060-0.313)	2.6 (2.1-3.8)

### Summary of National Kidney Foundation/Dialysis Outcomes Quality Initiative Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: Update 2000

- Epoetin alpha and beta are equivalent products, only alpha is licensed for sale in the USA.
- In hemodialysis patients, blood sample to document and monitor anemia should be obtained prior to or immediately upon initiation of the dialysis procedure.
- Target Hct level is 33-36% (Hgb 11-12 g/dl)
- Hemoglobin is a more accurate test to quantify anemia. Hgb is stable at room temperature and is not falsely elevated by hyperglycemia.
- Serum iron and the percent transferrin saturation reflect the amount of iron immediately available for hemoglobin synthesis. Serum ferritin reflects total body iron stores. A low level of either of these indices may indicate the need for supplemental iron to support erythropoiesis.
- There is a linear relationship between GFR and Hct, anemia has been noted when the GFR is between 20-35 ml/min/1.73 m<sup>2</sup>
- Reimbursement is available to dialysis centers for the use of epoetin when the Hct is  $\leq 36$ .
- Patient outcomes (mortality) are worse when Hgb is  $\leq 10$  g/dl. Higher Hct levels are associated with less LVH, higher quality of life, increased exercise capacity, lower incidence of hospitalization. Twenty three percent of patients need adjustment of antihypertensive medications as Hct levels increase.
- Dosing

Recommended Starting Dose of epoetin for anemia of chronic kidney disease	
	Units/kg/week Divide into 2-3 weekly doses
Subcutaneous	80-120
IV	120-180

- More frequent administration of Epoetin appears to be more efficient, two to three times per week appears to allow lower total weekly dose than administration once per week.
- When converting patients stabilized on IV dose to subcutaneous route use 2/3 of the weekly IV dose.

- If patients require < 3,000 units per week convert to once a week injections.
- Typical increases in Hgb (Hct) are 0.3 g/dl (0.5-1.5%) per week
- Strategies for initiating and converting to subcutaneous epoetin administration
  - Continue subcutaneous (SC) administration when patients begin dialysis
  - Establish a unit-wide policy of converting all patients to subcutaneous administration at the same time.
  - Educate patients on the advantages of SC administration.
  - Use the smallest needle possible (29 gauge)
  - Rotate injection sites between arm, thigh and abdominal wall.
  - Use the multidose vial when possible as benzyl alcohol acts as a local anesthetic.
- If administered intraperitoneal administer into a dry abdomen or with a small amount of dialysate (50 ml).
- Ninety six percent of patients will respond to epoetin at 100 units/kg SC three times weekly or 150 units/kg IV three times weekly.

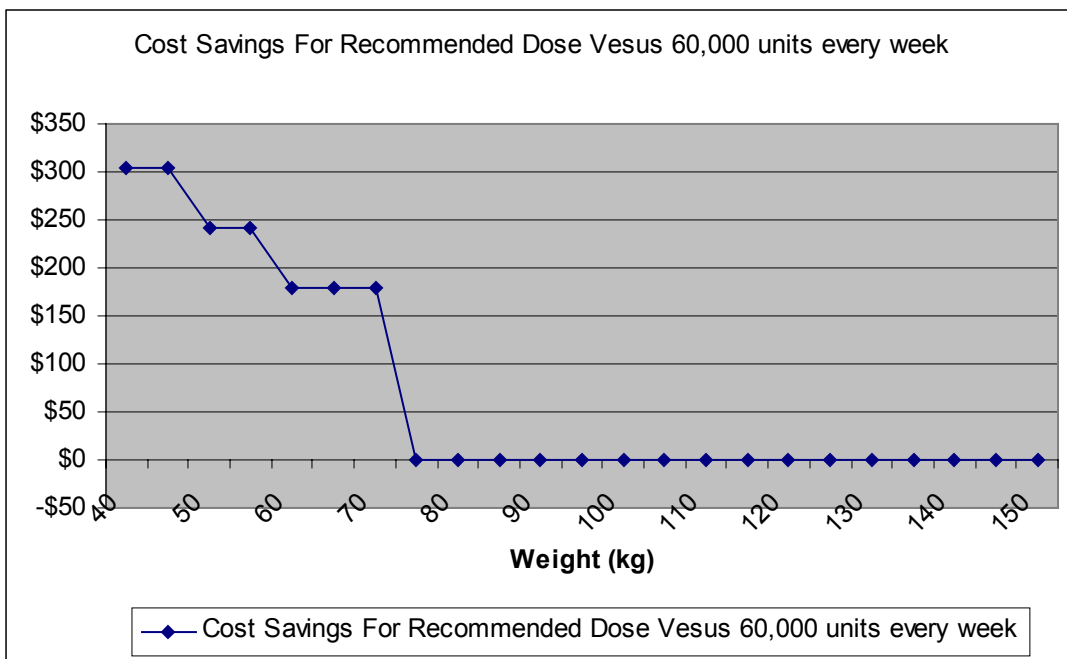
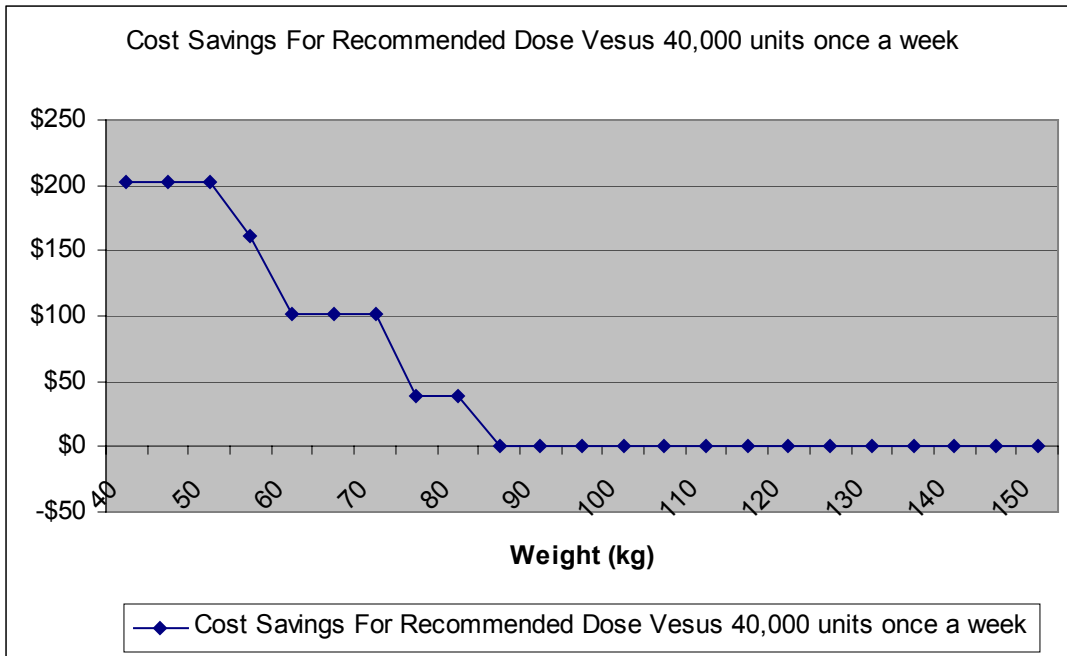
#### Iron Therapy

- Both iron and epoetin are required to produce red blood cells; as a result, unless adequate iron is available, epoetin will be relatively ineffective.
- Iron (blood) losses are high in hemodialysis patients.
- Oral iron usually cannot maintain adequate iron stores in hemodialysis patients receiving epoetin.
  - If used 200 mg of elemental iron per day is recommended.
  - Iron polysaccharide is no better tolerated (no less nausea, vomiting, or abdominal discomfort) than ionic iron salts (iron sulfate, fumarate, gluconate). Administer iron > 2 hours after meals and > than 1 hour before meals.
- Epoetin use often leads to functional iron deficiency.
- Functional and absolute iron deficiency may be prevented by regular use of small weekly doses of intravenous iron.
  - Sufficient iron should be administered to maintain a transferrin saturation  $\geq 20\%$  and a ferritin of  $\geq 100$  ng/ml. Transferrin saturation  $\geq 50\%$  and a ferritin of  $\geq 800$  ng/ml are unlikely to cause an increase in Hgb/Hct or decrease in epoetin dose required to maintain a given Hgb/Hct. If these levels are obtained, iron should be withheld for up to 3 months and levels remeasured before IV iron is resumed. Maintenance doses are usually 25-125 mg every week.
- Hgb/Hct, transferrin saturation and serum transferrin should be determined at least once every 3 months.
- % Transferrin saturation =  $\frac{\text{serum iron} \times 100}{\text{total iron binding capacity}}$ , reflects iron that is readily available for erythropoiesis.
- Serum ferritin reflects storage iron (liver, spleen and bone marrow reticuloendothelial cells)
- Absolute iron deficiency if serum ferritin is < 12 ng/ml or TSAT < 16% for normal patients.
- Absolute iron deficiency if serum ferritin is < 100 ng/ml or TSAT < 20% for hemodialysis patients.
- Functional iron deficiency results when iron needs are greater than can be release for iron stores (reticuloendothelial cells). TSAT decreases despite normal or elevated serum ferritin.
  - The half-life of epoetin by subcutaneous administration is 19-25 hours versus 5-11 hours when given by the IV route.

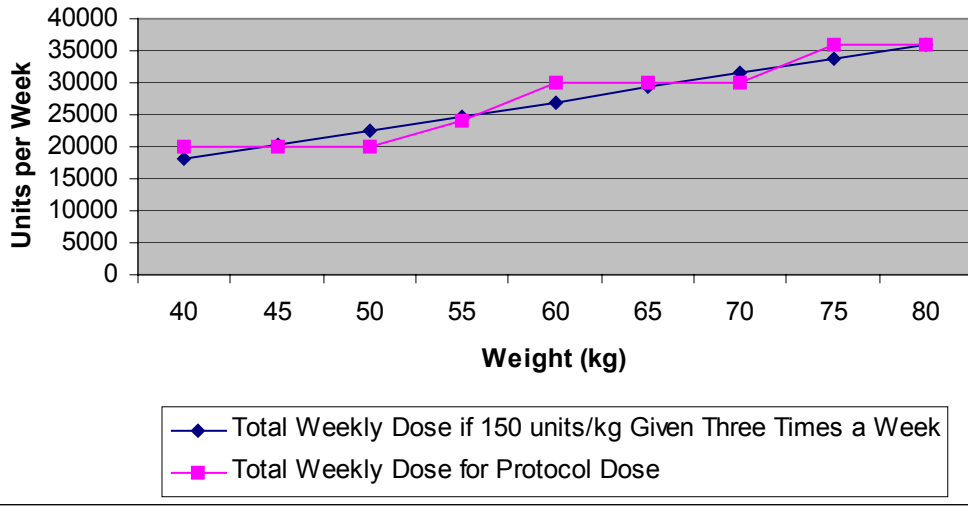
Epoetin Half-life		
	Subcutaneous	IV
Half-Life	19-25 hours	5-11 hours

#### Pharmacokinetic and Pharmacodynamics

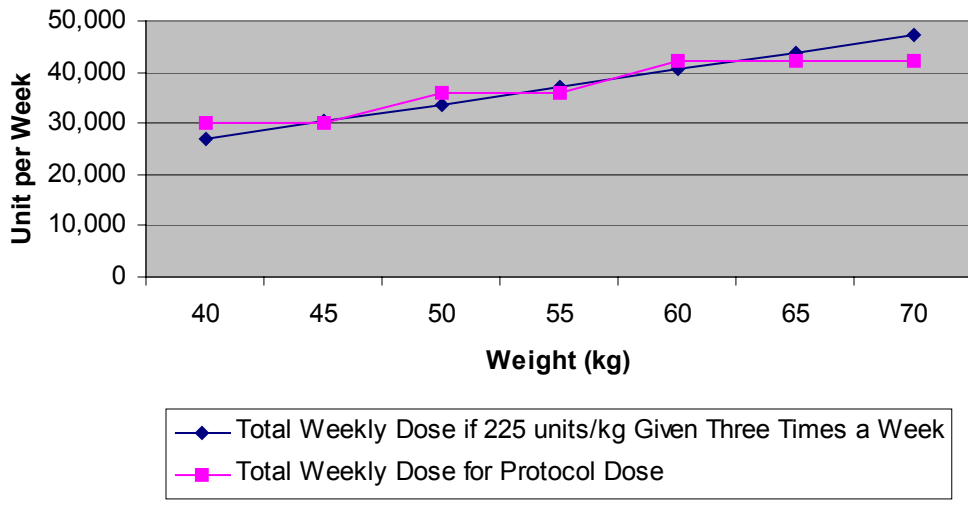
- The rate of rise in: Hgb, reticulocyte count, RBCs is the same for 150 units/kg three times a week or 40,000 units once a week.
- The pharmacodynamic responses of the three times weekly and once weekly dosing regimens are similar. Although the serum erythropoietin AUC for every week dosing is larger than that of three times a week dosing the AUC (reticulocytes), AUC (Hgb) and the AUC (RBC) are comparable. Serum erythropoietin levels for every week dosing drop below three times a week dosing 4 days post injection.
- Erythropoietin receptors in the progenitor cells in bone marrow are capable of being saturated.
- Erythropoiesis requires erythropoietin levels to be maintained above certain effective concentrations.



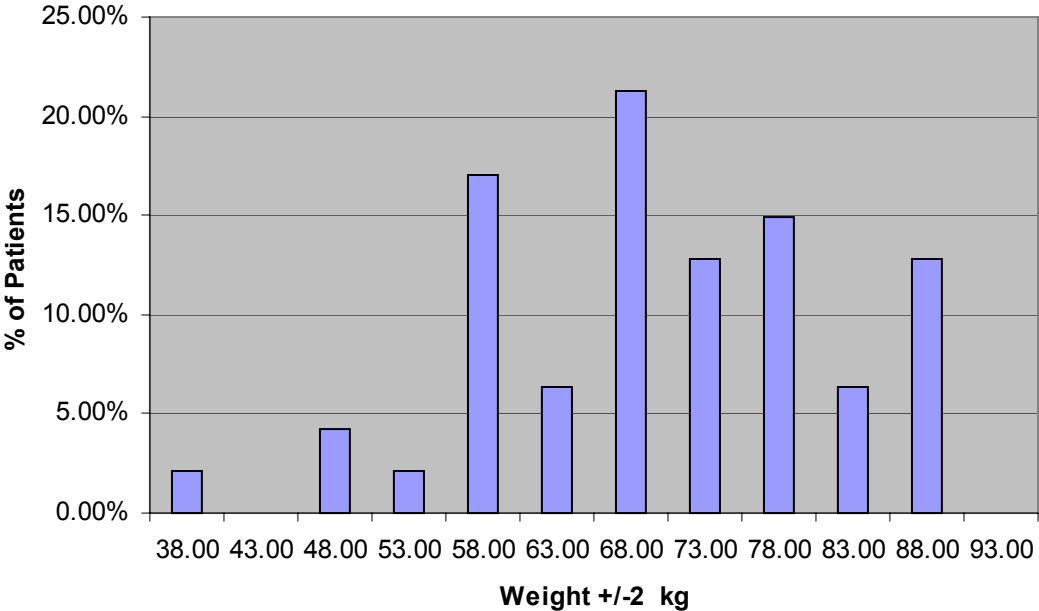
**Protocol Dose Versus 150 units/kg Three Times a Week for 40,000 units qweek**



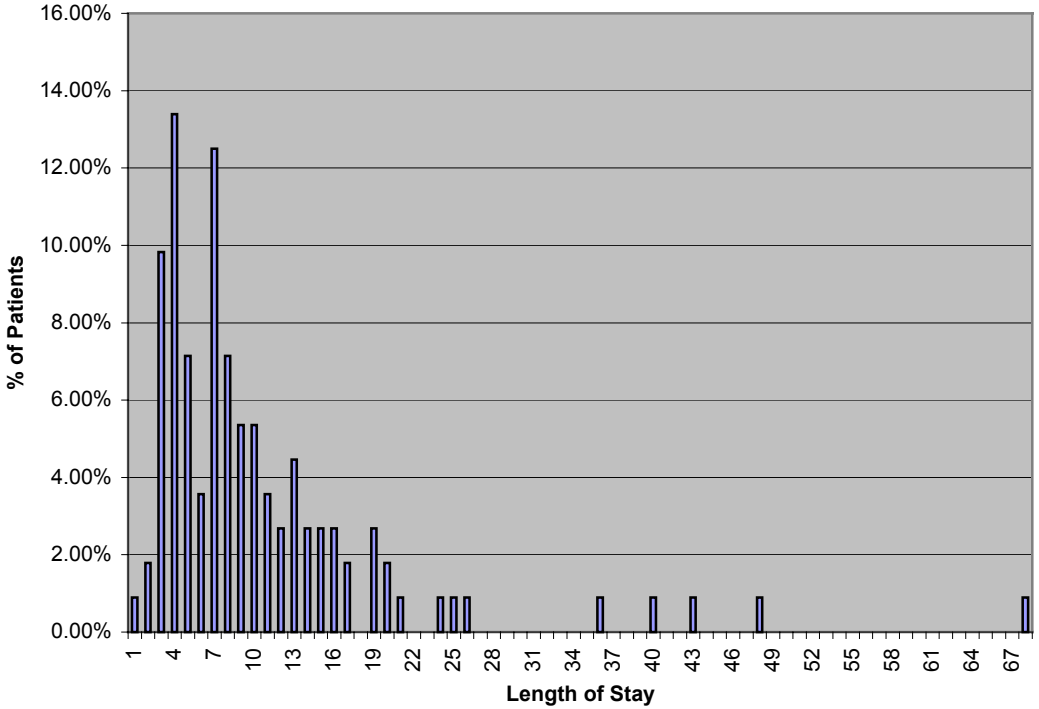
**Protocol Dose Versus 225 units/kg Three Times a Week for 60,000 units qweek**



**Histogram of Patient Weights**



**Length of Stay for Patients Receiving Epoetin (9/03-1/04)**



1. Blood. 2002 Oct 1; 100(7): 2303-20. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D, Djulbegovic B, Goode MJ, Jakubowski AA, Lee SJ, Miller CB, Rarick MU, Regan DH, Browman GP, Gordon MS; American Society of Clinical Oncology; American Society of Hematology. Medical College of Wisconsin, Milwaukee, WI 53226, USA. rizzo@mcw.edu

Anemia resulting from cancer or its treatment is an important clinical problem increasingly treated with the recombinant hematopoietic growth factor erythropoietin. To address uncertainties regarding indications and efficacy, the American Society of Clinical Oncology and the American Society of Hematology developed an evidence-based clinical practice guideline for the use of epoetin in patients with cancer. The guideline panel found good evidence to recommend use of epoetin as a treatment option for patients with chemotherapy-associated anemia with a hemoglobin (Hgb) concentration below 10 g/dL. Use of epoetin for patients with less severe anemia (Hgb level below 12 g/dL but never below 10 g/dL) should be determined by clinical circumstances. Good evidence from clinical trials supports the use of subcutaneous epoetin thrice weekly (150 U/kg) for a minimum of 4 weeks. Less strong evidence supports an alternative weekly (40 000 U/wk) dosing regimen, based on common clinical practice. With either administration schedule, dose escalation should be considered for those not responding to the initial dose. In the absence of response, continuing epoetin beyond 6-8 weeks does not appear to be beneficial. Epoetin should be titrated once the hemoglobin concentration reaches 12 g/dL. Evidence from one randomized controlled trial supports use of epoetin for patients with anemia associated with low-risk myelodysplasia not receiving chemotherapy; however, there are no published high-quality studies to support its use for anemia in other hematologic malignancies in the absence of chemotherapy. Therefore, for anemic patients with hematologic malignancies it is recommended that physicians initiate conventional therapy and observe hematologic response before considering use of epoetin.

- Guideline Recommendations Overview

1. Determine if the underlying cause of anemia is aside from chemotherapy or hematopoietic malignancy. Consider iron, folate, or B<sub>12</sub> deficiency and assess for occult blood loss.
2. If anemia is determined to be chemotherapy induced, begin red blood cell transfusion and/or epoetin when the patients' Hgb  $\leq$  10 g/dL.
3. Epoetin dosing: Starting dose of epoetin is 150 units/kg subcutaneously three times per week (TIW) for a minimum of 4 weeks. For patients that do not respond to the initial dose, escalate the dose to 300 units/kg subcutaneously TIW for an additional 4-8 weeks. In clinical practice, it is common and for convenience purposes, patients receive 40,000 units per week dosing. The TIW regimen has the most compelling evidence, and no randomized controlled clinical trials have reported to substantiate or contradict the outcome of once weekly (QW) versus TIW epoetin.
4. Epoetin dosing can be done either subcutaneously or intravenously. None of the studies included compared subcutaneous versus intravenous. Results from hemodialysis studies suggested that subcutaneous administration is more efficient than intravenous administration.
5. Epoetin response: Response to epoetin is considered to be at least 1-2 g/dL rise in Hgb 8 weeks from initiation. When the patient reaches a Hgb of 12 g/dL the epoetin dose can either be titrated to maintain the Hgb of 12 g/dL, or stopped and restarted when the Hgb begins to drop near 10 g/dL. If the patient does not respond, they should be evaluated for further tumor progression or iron deficiency.
6. Periodically, the patient's iron, total iron-binding capacity, transferrin saturation, or ferritin should be evaluated. This should be done to maximize the patients' epoetin response capacity, and limit the need of epoetin therapy.
7. For patients with hematologic malignancy—myelodysplasia, multiple myeloma, non-Hodgkin lymphoma, and chronic lymphocytic leukemia, there is limited data that supports the use of epoetin in these cases. There is only one, placebo-controlled, randomized trial that supports the use of patients with low-risk myelodysplasia. In the other cases, chemotherapy and/or corticosteroids should be used primarily before considering epoetin.

2. J Clin Oncol. 2001 Jun 1; 19(11): 2875-82. Comment in: J Clin Oncol. 2002 Feb 1; 20(3): 878 J Clin Oncol. 2002 Jul 15; 20(14): 3182-3; author reply 3183-4 J Clin Oncol. 2002 Jun 1; 20(11): 2757-8

Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E, Einhorn LH. Mount Sinai Medical Center, New York, NY 10029, USA. janice.gabrilove@mssm.edu

- PURPOSE: To prospectively evaluate the effectiveness, safety, and clinical benefits of once-weekly epoetin alfa therapy as an adjunct to chemotherapy in anemic cancer patients. PATIENTS AND METHODS: A total of 3,012 patients with nonmyeloid malignancies who received chemotherapy were enrolled onto this multicenter, open-label, nonrandomized study conducted in 600 United States community-based practices. Patients received epoetin alfa 40,000 U once weekly, which could be increased to 60,000 U once weekly after 4 weeks dependent on hemoglobin response. Treatment was continued for a maximum of 16 weeks. RESULTS: Among the 2,964 patients assessable for efficacy, epoetin alfa therapy resulted in significant increases in hemoglobin levels, decreases in transfusion requirements, and improvements in functional status and fatigue as assessed by the linear analog scale assessment (energy level, ability to perform daily activities, and overall quality of life) and the anemia subscale of the Functional Assessment of Cancer Therapy-Anemia questionnaire. Improvements in quality-of-life parameters correlated significantly (P <.001) with increased hemoglobin levels. The direct relationship between hemoglobin and quality-of-life improvement was sustained during the 16-week study period, which is similar to

findings of large community-based trials of three-times-weekly dosing. Once-weekly epoetin alfa was well tolerated, with most adverse events attributed to the underlying disease or concomitant chemotherapy. **CONCLUSION:** The results from this large, prospective, community-based trial suggest that once-weekly epoetin alfa therapy increases hemoglobin levels, decreases transfusion requirements, and improves quality of life in patients with cancer and anemia who undergo concomitant chemotherapy. Based on the results of this study, the clinical benefits and the adverse event profile of once-weekly epoetin alfa therapy in community-based practice are similar to those observed in the historical experience with the three-times-weekly dosage schedule. The response rate to 40,000 units once weekly is 49.2% and 68% to 60,000 units once weekly. Response was defined as increase in Hgb  $\geq 2$  g/dl or Hgb  $\geq 12$  g/dl, with no transfusions within previous 30 days.

**Inclusion Criteria:**

- 18 years of age
- Receiving chemotherapy for a non-myeloid malignancy
- Hgb < 11 g/dL
- Life expectancy of at least 6 month
- Ability to understand and provide written informed consent

**Exclusion Criteria:**

- Uncontrolled hypertension
- Known hypersensitivity to mammalian cell-derived or human albumin products
- Known history of anemia attributable to factors other than cancer or chemotherapy
- Previous epoetin alfa treatment
- Scheduled for bone marrow transplantation within 4 month
- Treatment with peripheral-blood progenitor cell therapy

Figure 1: Effect of once-weekly epoetin alfa therapy on hemoglobin levels. Data represent the mean hemoglobin levels for all patients and patients with breast, gynecologic, lung, and hematologic cancers during the 4-month study period. \*Statistically significant difference ( $P < .007$ ) from baseline; †statistically significant difference ( $P < .007$ ) from the previous month.

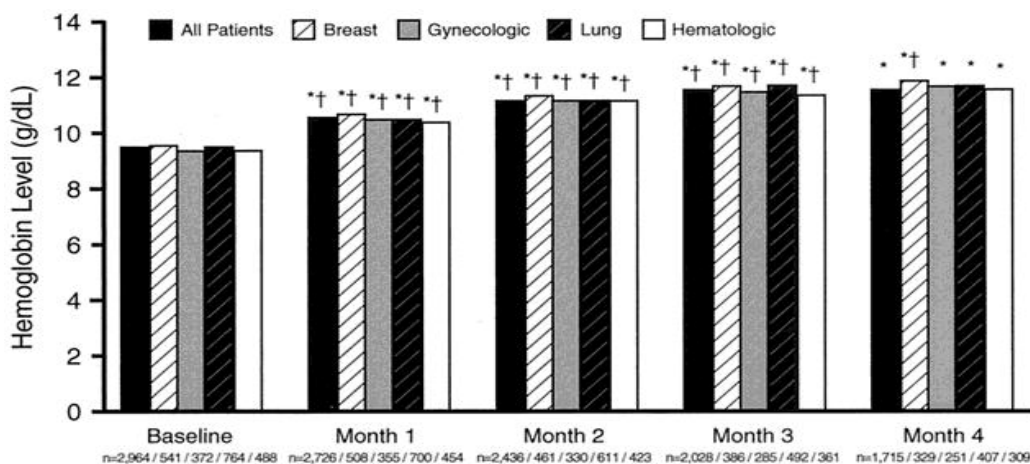
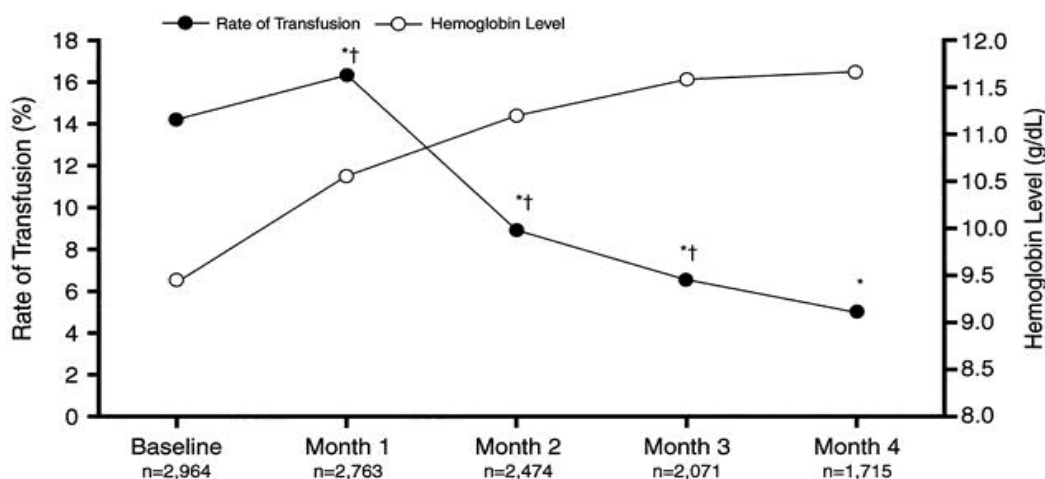


Fig 2. Percentage of patients transfused by month and hemoglobin level. \*Statistically significant difference ( $P < .007$ ) from baseline; †statistically significant difference ( $P < .007$ ) from the previous month.



3. J Clin Oncol. 2001 Jun 1; 19(11): 2865-74. Comment in: J Clin Oncol. 2002 Jan 15;20(2):601-3. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B; Epoetin Alfa Study Group John Radcliffe Hospital, Oxford, United Kingdom. tim.littlewood@orh.anglox.nhs.uk

**PURPOSE:** This randomized, double-blind, placebo-controlled clinical trial assessed the effects of epoetin alfa on transfusion requirements, hematopoietic parameters, quality of life (QOL), and safety in anemic cancer patients receiving non platinum chemotherapy. The study also explored a possible relationship between increased hemoglobin and survival. **PATIENTS AND METHODS:** Three hundred seventy-five patients with solid or non myeloid hematologic malignancies and hemoglobin levels  $\leq$  10.5 g/dL, or greater than 10.5 g/dL but  $\leq$  12.0 g/dL after a hemoglobin decrease of  $\geq$  1.5 g/dL per cycle since starting chemotherapy, were randomized 2:1 to epoetin alfa 150 to 300 IU/kg (n = 251) or placebo (n = 124) three times per week subcutaneously for 12 to 24 weeks. The primary end point was proportion of patients transfused; secondary end points were change in hemoglobin and QOL. The protocol was amended before unblinding to prospectively collect and assess survival data 12 months after the last patient completed the study. **RESULTS:** Epoetin alfa, compared with placebo, significantly decreased transfusion requirements (P = .0057) and increased hemoglobin (P < .001). Improvement of all primary cancer- and anemia-specific QOL domains, including energy level, ability to do daily activities, and fatigue, was significantly (P < .01) greater for epoetin alfa versus placebo patients. Although the study was not powered for survival as an end point, Kaplan-Meier estimates showed a trend in overall survival favoring epoetin alfa (P = .13, log-rank test), and Cox regression analysis showed an estimated hazards ratio of 1.309 (P = .052) favoring epoetin alfa. Adverse events were comparable between groups. **CONCLUSION:** Epoetin alfa safely and effectively ameliorates anemia and significantly improves QOL in cancer patients receiving nonplatinum chemotherapy. Encouraging results regarding increased survival warrant another trial designed to confirm these findings. Response was 70.5%, defined as increase in Hgb  $\geq$  2 g/dl.

**Inclusion Criteria:**

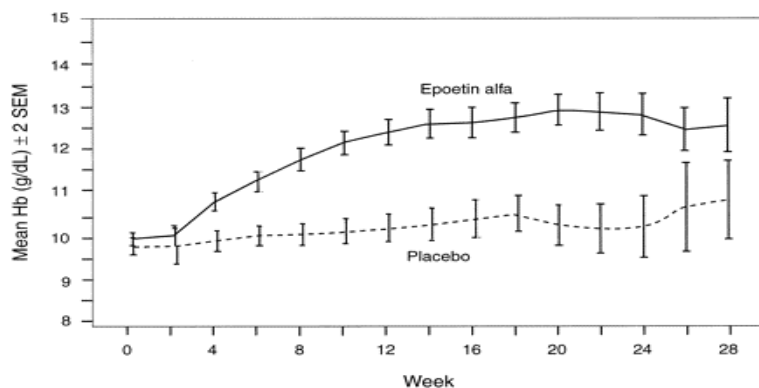
- At least 18 years of age
- Confirmed diagnosis of solid or nonmyeloid hematologic malignancy
- Receiving or scheduled to receive nonplatinum chemotherapy, with a minimum cycle duration of 3 weeks
- Life expectancy of at least 6 months
- Hgb  $\leq$  10.5 g/dL OR  $>$  10.5 g/dL but  $\leq$  12.0 g/dL after a 1.5 g/dL or greater decrease in Hgb level per cycle or month since beginning chemotherapy

**Exclusion Criteria:**

- No subject could have received a platinum-containing chemotherapy within 3 months of study enrollment.
- Patients with acute leukemia (lymphocytic or myelolytic) and myeloid malignancies
- Uncontrolled hypertension
- Untreated iron, folate, or vitamin B<sub>12</sub> deficiency
- Patients that had undergone myeloablative chemotherapy or acute infection or bleeding within 1 month
- Patients that had undergone radiotherapy or allogeneic blood transfusion within 14 days
- Patients that had a severe illness or surgery within 7 days of study entry

**Graphics:**

Fig 1. Mean biweekly hemoglobin (Hgb) levels for all patients treated with epoetin alfa or placebo (EFF population). Missing values at any evaluation point are replaced by last value carried forward.



4. Cardiovasc Res. 2003 Sep 1;59(3):538-48. The cardiovascular effects of erythropoietin Smith KJ, Bleyer AJ, Little WC, Sane DC. Section of Cardiology, Department of Internal Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1045, USA.

Erythropoietin is a hypoxia-induced hormone that is essential for normal erythropoiesis. The production of recombinant human erythropoietin (rHuEpo) has revolutionized the treatment of anemia associated with chronic renal failure and chemotherapy, and has been used as prophylaxis to prevent anemia after surgery. The erythropoietin receptor is widely distributed in the cardiovascular system, including endothelial cells, smooth muscle cells and cardiomyocytes. Epo has potentially beneficial effects on the endothelium including anti-apoptotic, mitogenic and angiogenic activities. On the other hand, some reports suggest that rHuEpo may have pro-thrombotic or platelet-activating effects. Hypertension develops in 20-30% of renal patients treated with rHuEpo. Many patients with heart failure have anemia. Despite some potential adverse effects, early studies in heart failure patients with anemia suggest that rHuEpo therapy is safe and effective in reducing left ventricular hypertrophy, enhancing exercise performance and increasing ejection fraction. Further studies are warranted to define the role of rHuEpo in chronic heart failure and other cardiovascular settings.

Table 1  
Cellular effects of erythropoietin

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*Platelets*

Increased production of microparticles  
Enhanced platelet activation

*Vascular endothelium*

Mitogenic, chemotactic and angiogenic effect  
Increased endothelin production  
Increased PAI-1 production

*Vascular smooth muscle*

Raises cytosolic  $Ca^{2+}$  concentration  
Increases responses to norepinephrine, angiotensin II, and endothelin-1  
Mitogenic effect

*Cardiomyocytes*

Enhances proliferation (neonatal)  
Stimulates  $Na^+$ ,  $K^+$  activity

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The effects of Epo on cellular components of the cardiovascular system are summarized.

5. Med Oncol. 1998 Sep;15(3):174-82. Comment in: Med Oncol. 1998 Sep;15(3):141-4. Controlled multicentre study of the influence of subcutaneous recombinant human erythropoietin on anaemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based chemotherapy. ten Bokkel Huinink WW, de Swart CA, van Toorn DW, Morack G, Breed WP, Hillen HF, van der Hoeven JJ, Reed NS, Fairlamb DJ, Chan SY, Godfrey KA, Kristensen GB, van Tinteren H, Ehmer B. The Netherlands Cancer Institute, Amsterdam, The Netherlands. [wthb@nki.nl](mailto:wthb@nki.nl)

This randomized controlled multicentre trial evaluated the effectiveness of recombinant human erythropoietin (rhEPO) in preventing anaemia and reducing the need for blood or erythrocyte transfusion in 122 ovarian cancer patients receiving platinum-based chemotherapy. The patients were randomly allocated to receive rhEPO 150 U/kg or 300 U/kg subcutaneously, three times a week, or open control. Patients also received up to 6 cycles of carboplatin or cisplatin, alone or in combination with other cytotoxic agents. Intention-to-treat analysis showed that 39.4% of patients in the control group received at least one blood transfusion, compared with 9.2% of patients treated with rhEPO. Patients treated with rhEPO experienced a significantly longer time to first erythrocyte transfusion than the control group and were less likely to experience nadir haemoglobin levels  $< 10$  g/dl ( $P < 0.001$  and  $< 0.05$ , respectively). A haemoglobin decrease  $< 1$  g/dl during the first chemotherapy cycle, as well as a low baseline serum erythropoietin concentration, predicted a low transfusion need in rhEPO-treated patients but not in controls. During the study, 103 patients suffered at least one adverse event, but no serious, and only nine non-serious adverse events were considered possibly related to rhEPO therapy. These results indicate that treatment with rhEPO prevents anaemia, it reduces the need for blood or rhEPO erythrocyte transfusion in patients with ovarian cancer receiving platinum-based chemotherapy, and it is well tolerated. A starting dose of 150 U/kg of rhEPO, three times a week, may be recommended. *Epoetin dosage progressively decreased in both treatment groups during the study, 150 units/kg to 129 units/kg three times a week and 300 units/kg to 154 units/kg three times a week.*

Inclusion Criteria:

- 18 years of age
- Ovarian Carcinoma, Stage IIb-IV
- Performance status = 0-2, according to WHO
- Hgb  $< 13$  g/dL, prior to treatment (average entry Hgb 11.8 g/dl)

- Life expectancy > 2 months
- Previously treated patients who had achieved a complete remission, and had not received treatment for at least 1 year
- Receiving cisplatin  $\geq 75 \text{ mg/m}^2$  or carboplatin  $\geq 350 \text{ mg/m}^2$

Exclusion Criteria:

- Prior chemotherapy or radiotherapy for ovarian cancer, that did not meet the above inclusion criteria
- $\text{WBC} \leq 3.5 \times 10^9 /\text{L}$
- Platelet count  $\leq 100 \times 10^9 /\text{L}$
- Hypertension (SBP > 160 mmHg, DBP > 95 mmHg)
- Impaired liver function (Bilirubin >25 mmol/L)
- Impaired renal function (Cr > 120  $\mu\text{mol/L}$ )
- Thrombocytosis ( $\geq 500 \times 10^9 /\text{L}$ )
- Other reasons for anemia
- Severely impaired coagulation
- Iron deficiency
- Epilepsy
- Blood transfusion less than 1 week prior to protocol treatment
- Hemoglobinopathies
- Acute infections
- Second primary tumors
- Administration of any investigational drug within 30 days preceding the first dose of the study drug

6. Br J Cancer. 1999 May;80(3-4):396-402. Epoetin alpha prevents anaemia and reduces transfusion requirements in patients undergoing primarily platinum-based chemotherapy for small cell lung cancer. Thatcher N, De Campos ES, Bell DR, Steward WP, Varghese G, Morant R, Vansteenkiste JF, Rosso R, Ewers SB, Sundal E, Schatzmann E, Stocker H. CRC Department of Oncology, Christie Hospital NHS Trust, Manchester, UK.

Anaemia commonly occurs in cancer patients receiving chemotherapy, often necessitating blood transfusion. This multicentre study was designed to evaluate the efficacy and safety of epoetin alpha in preventing the decline in haemoglobin (Hgb) level, and to determine whether the transfusion requirement could be reduced, in patients receiving 4-6 cycles of primarily platinum-based combination cyclic chemotherapy for small cell lung cancer (SCLC). A total of 130 non-anemic SCLC patients were randomized to receive no additional treatment (n = 44), epoetin alpha 150 IU kg(-1) subcutaneously (s.c.) three times a week (n = 42) or 300 IU kg(-1) s.c. three times a week (n = 44). Reductions in epoetin alpha dosage were made during the study if Hb level increased to >15 g l(-1). The mean weekly dosage was 335 and 612 IU kg(-1), respectively, in the two active treatment groups. Significantly fewer (P < 0.05) epoetin alpha-treated patients experienced anaemia (Hb < 10 g dl(-1)) during the course of chemotherapy (300 IU kg(-1), 39%; 150 IU kg(-1), 48%; untreated, 66%). This was reflected in the significantly lower number of treated patients transfused [300 IU kg(-1), 20% (P < 0.001); 150 IU kg(-1), 45% (P < 0.05); untreated, 59%]. Epoetin alpha was well-tolerated, and there was no evidence of sustained, clinically significant, hypertension. In summary, epoetin alpha is effective and well-tolerated in maintaining Hb level and reducing transfusion requirement in patients undergoing cyclic chemotherapy for SCLC. A starting dose of 150 units/kg three times a week is recommended.

Inclusion Criteria:

- 18-75 years of age
- Planned treatment for combination chemotherapy, primarily platinum based, for 4-6 cycles for SCLC
- Ambulatory, capable of self care according to WHO
- Hgb level  $\geq 10.5 \text{ g/dL}$
- Neutrophil count >  $3000 \text{ mm}^{-3}$
- Platelet count >  $100,000 \text{ mm}^{-3}$
- No clinically relevant abnormalities of renal or hepatic function
- Serum calcium < 10.6 mg/dL
- Negative for occult blood

Exclusion Criteria:

- Pregnant or of childbearing potential and not taking adequate contraceptive measures
- Clinically significant disease
- History of primary hematological disease
- Anemia attributable to factors other than cancer or chemotherapy
- Cerebral metastases
- Uncontrolled hypertension
- History of seizures
- Acute illness within 7 days of study entry
- Androgen therapy within 2 months of study entry

- Received any experimental treatment, immunosuppressive drugs, or other drugs that affect hematocrit within 1 month prior to study entry
- Receiving hematopoietic growth factors
- Participating in another clinical trial

7. Clin Pharmacol Ther. 1998 Oct;64(4):412-23. Pharmacokinetics and pharmacodynamics of recombinant human erythropoietin after single and multiple subcutaneous doses to healthy subjects. Cheung WK, Goon BL, Guilfoyle MC, Wacholtz MC. Department of Drug Metabolism, R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ 08869-0602, USA.

**OBJECTIVES:** To understand the pharmacokinetic and pharmacodynamic properties of recombinant human erythropoietin (epoetin alfa) and to continue to optimize dosing regimens by determining whether administration of single high doses of epoetin alfa is as effective as repeated administration. **METHODS:** Epoetin alfa was administered as single subcutaneous doses of 300, 450, 600, 900, 1200, 1350, 1800, and 2400 IU/kg and in multiple subcutaneous dose regimens: 150 IU/kg 3 times a week for 4 weeks and 600 IU/kg once per week for 4 weeks in 2 open-label, randomized placebo-controlled studies in healthy volunteers. **RESULTS:** The absorption rate of epoetin alfa after subcutaneous administration was independent of dose, whereas clearance was dose-dependent in that it decreased with increasing dose. There was a linear relationship between response measured as percentage of reticulocyte area under the curve (AUC) and erythropoietin AUC for single doses up to 1800 IU/kg. Beyond the 1800 IU/kg dose, there was a saturation of response. The mean percentage of reticulocytes after single-dose regimens began to increase by days 3 to 4, reached their maximum at days 8 to 11, and returned to baseline values by day 22. In contrast, the mean percentage of reticulocytes after both multiple-dose regimens were maintained above baseline values through day 22 as both regimens stimulated modest but sustained increases in percentage of reticulocytes (1% to 2%). The mean percentage of reticulocytes AUC for 600 IU/kg epoetin alfa given once a week for 4 weeks was apparently greater than the mean percentage of reticulocytes AUC for 150 IU/kg 3 times a week for 4 weeks. Although daily oral iron supplementation was given, mean serum ferritin levels declined by approximately 75% through day 22 in subjects treated with multiple doses of epoetin alfa. **CONCLUSIONS:** These findings show that the pharmacologic response to epoetin alfa is a function of dose and dosing regimen. Repeated administration of epoetin alfa was more effective in stimulating a reticulocyte response than single-dose administration of the same total amount of epoetin alfa.

**Inclusion Criteria:**

- Male
- 18-45 years of age
- 63.6-100 kg
- Pre-randomization hemoglobin and hematocrit values between 13.8-16.4 g/dL and 41-49%, respectively
- Pre-randomization reticulocytes  $\leq$  3%
- Normal iron parameters, including, ferritin  $<$ 18 ng/mL, iron/total iron binding capacity ratio  $<$ 12%, and normal serum folate and vitamin B<sub>12</sub>

**Exclusion Criteria:**

- Evidence of pulmonary, cardiovascular, neurologic, endocrine, gastrointestinal, genitourinary, or other body systems dysfunction
- Acute illness within 7 days of study entry or a major infection
- Chronic medical condition that required prescription medication
- Androgen therapy within 2 months of randomization
- Consumption of an experimental drug or therapy within 30 days of study entry
- Consumption of any medications within the last 2 weeks other than acetaminophen
- History of hemolytic anemia
- History of gastrointestinal bleeding
- Baseline serum erythropoietin level  $>$  30 mIU/mL
- Known sensitivity to mammalian-derived products, human serum albumin, or components of the study medication
- History of smoking

**Conclusion:** The administration of a single large dose of epoetin is not as effective in stimulating a reticulocyte response as administration of the same total amount of epoetin alfa given at lower intermittent doses.

8. Eur J Clin Pharmacol. 2001 Aug;57(5):411-8. Pharmacokinetics and pharmacodynamics of epoetin alfa once weekly and three times weekly. Cheung W, Minton N, Gunawardena K. The R W Johnson Pharmaceutical Research Institute, Raritan, NJ 08869, USA. **OBJECTIVE:** To compare the pharmacokinetics, pharmacodynamics, and tolerance of epoetin alfa administered subcutaneously (s.c.) once weekly (q.w.) and three times weekly (t.i.w.). **METHODS:** An open-label, randomized, parallel-design study was conducted in 36 healthy adults with hemoglobin (Hb) levels of 11.7-14.0 g/dl for women and 13.0-14.8 g/dl for men. Subjects were randomized to epoetin alfa 150 IU/kg s.c. t.i.w. or 40,000 IU s.c. q.w. for 4 weeks. Serum erythropoietin concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA). Pharmacokinetic parameters [peak serum concentration (C<sub>max</sub>), mean predose trough concentration (C<sub>min</sub>), time to C<sub>max</sub> (t<sub>max</sub>), clearance after s.c. administration (CL/F), area under the plasma concentration time curve (AUC), and terminal elimination half-life (t<sub>1/2</sub>)] were calculated using model-independent methods. Mean changes from baseline and AUC of percentage reticulocytes, Hb, and total red blood cell (RBC) concentrations over the 1-month

study period were calculated. RESULTS: The C<sub>max</sub> values for serum epoetin alfa q.w. were six times and AUC(0-168) values three times that of the t.i.w. regimen. Time profiles of changes in percentage reticulocytes, Hb, and total RBC over 1 month was similar between regimens. The rate of increase in Hb was similar for the two groups, and both groups exhibited a 3.1-g/dl increase in mean Hb levels from baseline through day 29. Changes in ferritin levels were generally similar between groups and reflected expected use of iron stores for Hb production. Epoetin alfa administered t.i.w. or q.w. was well-tolerated and no serious adverse events occurred. CONCLUSION: The pharmacodynamic responses were equivalent between groups despite expected differences in total erythropoietin exposure. These results indicate that the epoetin alfa 150 IU/kg t.i.w. and 40,000 IU q.w. regimens can be considered clinically equivalent.

Inclusion Criteria:

- 18-45 years of age
- Hgb between 12.0-14.0 g/dL, for women, and between 13.0-14.0 g/dL for men
- If female, postmenopausal, incapable of childbearing, or practicing an acceptable method of birth control that had to be continued during the study
- Ideal weight for height and body size +/- 15%
- A negative stool occult blood test
- Normal iron parameters, serum folate, and vitamin B<sub>12</sub> levels
- Nonsmoking
- Ability to restrain from consuming alcohol during the study period

Exclusion Criteria:

- History of a disease/dysfunction of a body system
- Hemolytic anemia, gastrointestinal bleeding, thrombosis and/or pulmonary embolism
- Chronic medical condition requiring prescription medications
- Androgen therapy within 2 months of randomization
- Blood donation within the past 90 days
- Percentage reticulocytes  $\geq 3.0\%$
- Serum erythropoietin level  $\geq 30$  mIU/mL
- Previous exposure to recombinant human erythropoietin

Conclusion: The pharmacodynamic responses were equivalent between groups. The doses can be considered clinically equivalent.

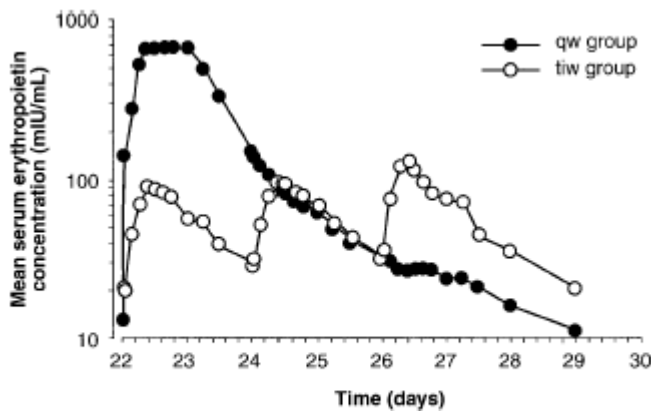


Fig. 1 Mean serum erythropoietin concentration–time profiles for epoetin alfa dosing regimens during the fourth dosing week

**Table 2** Mean pharmacokinetic parameters.  $C_{max}$  peak serum concentration,  $C_{min}$  mean predose trough concentration,  $t_{max}$  time to  $C_{max}$ ,  $CL/F$  clearance after subcutaneous administration,  $AUC$  area under the plasma concentration-time curve,  $t_{1/2}$  terminal elimination half-life,  $ND$  not determined, %  $CV$  percentage coefficient of variation, *t.i.w.* three times weekly, *q.w.* once weekly

Parameter	Epoetin alfa, 150 IU/kg t.i.w. (n = 17)		Epoetin alfa, 40,000 IU q.w. (n = 17)		Ratio <sup>a</sup>
	Mean (± SD)	% CV	Mean (± SD)	% CV	
$C_{max}$ (mIU/ml)	143 ± 54.2	37.8	861 ± 445.1	51.7	6.02
$C_{min}$ (mIU/ml)	18 ± 9.3	50.7	3.8 ± 4.27	114	0.21
$t_{max}$ (h)	ND		16 ± 7.5	45.6	ND
$AUC_{(0-168)}$ (mIU·h/ml)	8587 ± 1521.3	17.7	25,750 ± 9062.3	35.2	3.00
$CL/F$ (ml/h/kg)	54.1 ± 10.13	18.7	24.7 ± 7.19	29.1	0.46

<sup>a</sup>Ratios of 40,000 IU q.w. to 150 IU/kg t.i.w. mean parameter values

9. N Engl J Med. 1998 Aug 27;339(9):578-83. Comment in N Engl J Med. 1998 Aug 27;339(9):625-7. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients. Kaufman JS, Reda DJ, Fye CL, Goldfarb DS, Henderson WG, Kleinman JG, Vaamonde CA. Boston Veterans Affairs Medical Center and Department of Medicine, Boston University School of Medicine, MA 02130, USA.

**BACKGROUND:** Several studies have suggested that if recombinant human erythropoietin (epoetin) is administered subcutaneously rather than intravenously, a lower dose may be sufficient to maintain the hematocrit at a given level. **METHODS:** In a randomized, unblinded trial conducted at 24 hemodialysis units at Veterans Affairs medical centers, we assigned 208 patients who were receiving long-term hemodialysis and epoetin therapy to treatment with either subcutaneous or intravenous epoetin. The dose was initially reduced until the hematocrit was below 30 percent and then was gradually increased to a level that would maintain the hematocrit in the range of 30 to 33 percent for 26 weeks. We compared the average doses in the 26-week maintenance phase and the discomfort associated with the two routes of administration. **RESULTS:** For the 107 patients treated by the subcutaneous route, the average weekly dose of epoetin during the maintenance phase was 32 percent less than that for the 101 patients treated by the intravenous route (mean [+/-SD], 95.1+/-75.0 vs. 140.3+/-88.5 U per kilogram of body weight per week;  $P < 0.001$ ). Only one patient in the subcutaneous-therapy group withdrew from the study because of pain at the injection site, and 86 percent rated the pain associated with subcutaneous administration as ranging from absent to mild. **CONCLUSIONS:** In patients receiving hemodialysis, subcutaneous administration of epoetin can maintain the hematocrit in a desired target range, with an average weekly dose of epoetin that is lower than with intravenous administration.

**Inclusion Criteria:**

- ESRD
- Treated by hemodialysis for at least six month
- Received epoetin for at least three months before study entry
- Hct = 30-33% while receiving epoetin subcutaneously or intravenously thrice weekly during the week before randomization
- Serum ferritin > 100 ng/mL
- Serum transferrin saturation > 20%

**Exclusion Criteria**

- Uncontrolled hypertension
- Acute inflammatory disease
- Infection
- Hematological disorder
- Gastrointestinal bleeding
- Received a blood transfusion in the previous 8 weeks
- Sensitivity or resistance to epoetin
- Requiring a dose of epoetin < 30 units/kg of body weight per week
- Requiring a dose of epoetin > 500 units/kg of body weight per week

\*\* If the Hct value was outside the target range at the initial screening or the patient was receiving epoetin fewer than three times per week, the dose was adjusted before randomization

Figure 1: Average Epoetin Doses during the Maintenance Phase in the Subcutaneous-Therapy and Intravenous-Therapy Groups. Values represent the cumulative percentage of patients on the y axis requiring a dose of epoetin that was equal to or less than each value on the x axis.

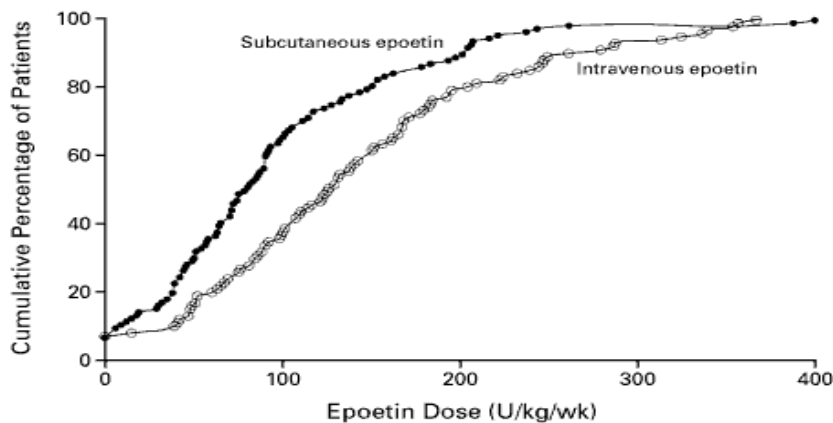


TABLE 2. RESULTS DURING THE MAINTENANCE PHASE OF SUBCUTANEOUS AND INTRAVENOUS EPOETIN THERAPY.\*

VARIABLE	SUBCUTANEOUS-THERAPY GROUP (N=107)	INTRAVENOUS-THERAPY GROUP (N=101)	P VALUE
Weekly maintenance dose of epoetin			
Average (U/kg/wk)	95.1±75.0	140.3±88.5	<0.001
Average (U/wk)	7397±6139	10,068±6334	0.002
Average hematocrit (%)	31.3±2.9	31.1±2.5	0.60
Average hemoglobin (g/dl)	10.4±1.0	10.3±0.9	0.21

\*Plus-minus values are means ±SD.

10. Nephrol Dial Transplant. 1995;10 Suppl 6:40-3. Subcutaneous versus intravenous administration of erythropoietin improves its efficiency for the treatment of anemia in haemodialysis patients. Albitar S, Meulders Q, Hammoud H, Soutif C, Bouvier P, Pollini J. Hopital Henri Duffaut, Department of Nephrology, Avignon, France.

Recombinant human erythropoietin (rHuEpo) seems to be more efficient when given subcutaneously (SC) instead of intravenously (IV) for therapy of anaemia in haemodialysis patients. This was a cross-over study designed to assess the efficiency of rHuEpo when given SC rather than IV in a 1 year follow-up. Sixteen patients received IV rHuEpo for 6 months, then SC rHuEpo for 6 months. They were four males and 12 females with a mean age of 56 years (range 15-82). Haemoglobin concentration ([Hb]) was kept at 10 g/dl and transferrin saturation (TS) at more than 25%. Mean [Hb] was 9.7 +/- 1.0 g/dl with IV rHuEpo and 9.9 +/- 0.9 g/dl with SC rHuEpo (NS). Transferrin saturation was 27% before rHuEpo, 31% with IV rHuEpo and 34% with SC rHuEpo (NS vs IV rHuEpo). Serum ferritin was 691 +/- 113 ng/ml before rHuEpo, 652 +/- 94 ng/ml with IV rHuEpo and 997 +/- 132 ng/ml with SC rHuEpo (P < 0.05 vs IV rHuEpo). Intact parathyroid hormone was 354 +/- 83 pg/ml before rHuEpo, 201 +/- 63 pg/ml with IV rHuEpo and 122 +/- 33 pg/ml with SC rHuEpo (NS vs IV rHuEpo). Doses of IV rHuEpo were 156 +/- 24 U/kg/week and SC rHuEpo 74 +/- 13 U/kg/week (i.e. a saving of 53%; P < 0.001). We conclude that subcutaneous administration of rHuEpo is twice as efficient as IV rHuEpo in patients with good functional iron reserve.

11. Nephrol Dial Transplant. 1995;10 Suppl 6:40-3. Subcutaneous versus intravenous administration of erythropoietin improves its efficiency for the treatment of anaemia in haemodialysis patients. Albitar S, Meulders Q, Hammoud H, Soutif C, Bouvier P, Pollini J. Hopital Henri Duffaut, Department of Nephrology, Avignon, France. Recombinant human erythropoietin (rHuEpo) seems to be more efficient when given subcutaneously (SC) instead of intravenously (IV) for therapy of anaemia in haemodialysis patients. This was a cross-over study designed to assess the efficiency of rHuEpo when given SC rather than IV in a 1 year follow-up. Sixteen patients received IV rHuEpo for 6 months, then SC rHuEpo for 6 months. They were four males and 12 females with a mean age of 56 years (range 15-82). Haemoglobin concentration ([Hb]) was kept at 10 g/dl and transferrin saturation (TS) at more than 25%. Mean [Hb] was 9.7 +/- 1.0 g/dl with IV rHuEpo and 9.9 +/- 0.9 g/dl with SC rHuEpo (NS). Transferrin saturation was 27% before rHuEpo, 31% with IV rHuEpo and 34% with SC rHuEpo (NS vs IV rHuEpo). Serum ferritin was 691 +/- 113 ng/ml before rHuEpo, 652 +/- 94

ng/ml with IV rHuEpo and 997 +/- 132 ng/ml with SC rHuEpo ( $P < 0.05$  vs IV rHuEpo). Intact parathyroid hormone was 354 +/- 83 pg/ml before rHuEpo, 201 +/- 63 pg/ml with IV rHuEpo and 122 +/- 33 pg/ml with SC rHuEpo (NS vs IV rHuEpo). Doses of IV rHuEpo were 156 +/- 24 U/kg/week and SC rHuEpo 74 +/- 13 U/kg/week (i.e. a saving of 53%;  $P < 0.001$ ). We conclude that subcutaneous administration of rHuEpo is twice as efficient as IV rHuEpo in patients with good functional iron reserve.