Reference number(s)
1983-A

Standard Medicare Part B Management Epogen-Procrit-Retacrit

Products Referenced by this Document

Drugs that are listed in the following table include both brand and generic and all dosage forms and strengths unless otherwise stated. Over-the-counter (OTC) products are not included unless otherwise stated.

Brand Name	Generic Name
Epogen	epoetin alfa
Procrit	epoetin alfa
Retacrit	epoetin alfa-epbx

Indications

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-approved Indications[1-3]

- Epoetin alfa is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion.
- Epoetin alfa is indicated for the treatment of anemia due to zidovudine administered at less than or equal to 4200 milligrams (mg) per week in patients with HIV-infection with endogenous serum erythropoietin levels of less than or equal to 500 milliunits per milliliter (mUnits/mL).
- Epoetin alfa is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
- Epoetin alfa is indicated to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin greater than 10 to less than or equal to 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery. Epoetin alfa is not indicated for patients who are willing to donate autologous blood preoperatively.

Limitations of Use

- Epoetin alfa has not been shown to improve quality of life, fatigue, or patient well-being.

- Epoetin alfa is not indicated for use:
    - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
    - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
    - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
    - In patients scheduled for surgery who are willing to donate autologous blood.
    - In patients undergoing cardiac or vascular surgery.
    - As a substitute for RBC transfusions in patients who require immediate correction of anemia.

Note: Use in members on dialysis is covered under the Medicare Part B dialysis benefit and is excluded from coverage under this policy.

Compendial Uses

- Anemia in members with myelodysplastic syndromes (MDS)[4,5,22,24]
- Anemia in epidermolysis bullosa[5,9]
- Anemia in congestive heart failure[5,25]
- Anemia due to critical illness[5,26]
- Anemia due to hepatitis C treatment with ribavirin in combination with either interferon alfa or peginterferon alfa[5,12]
- Anemia in porphyria cutanea tarda[5,22]
- Anemia in patients who will not/cannot receive blood transfusions[5,11,12]
- Prophylaxis of anemia of prematurity[5,21]
- Iron overload[5,15]
- Myelofibrosis-associated anemia[4,5,7,13]
- Anemia due to radiation[5,14]
- Anemia due to puerperium[5,16]
- Cancer patients who are undergoing palliative treatment[4,22]
- Blood unit collection for autotransfusion[5,18,19]

Nationally Covered Indication[8]

Centers for Medicare and Medicaid Services guidelines provide coverage for epoetin alfa for anemia secondary to myelosuppressive chemotherapy based on the criteria in the Exclusions, Coverage Criteria, and Continuation of Therapy sections.

All other indications will be assessed on an individual basis. Submissions for indications other than those listed in this criteria should be accompanied by supporting evidence from Medicare approved compendia.

Exclusions

The following exclusions criteria apply to members requesting use for anemia due to concomitant myelosuppressive chemotherapy:

- The anemia is due to folate, B-12, or iron deficiency.
- The anemia is due to hemolysis, bleeding, or bone marrow fibrosis.
- The anemia is due to treatment for acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), or erythroid cancers.
- The anemia of cancer is not related to cancer treatment.
- The anemia is due to treatment with radiotherapy only.
- Prophylactic use to prevent chemotherapy-induced anemia.
- Prophylactic use to reduce tumor hypoxia.
- Use in members with erythropoietin-type resistance due to neutralizing antibodies.
- Members with uncontrolled hypertension.

Coverage Criteria

Note: Requirements regarding hemoglobin level exclude values due to a recent transfusion.

Anemia Due to Chronic Kidney Disease[1-3]

Authorization of 12 weeks may be granted for the treatment of anemia due to chronic kidney disease in members not receiving dialysis with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

Anemia Due to Concomitant Myelosuppressive Chemotherapy[1-3,8,22,23]

Authorization of 8 weeks may be granted for the treatment of anemia due to concomitant chemotherapy in members when all of the following criteria are met:

- The member is receiving chemotherapy for a solid tumor, multiple myeloma, lymphoma, or lymphocytic leukemia.
- The hemoglobin level immediately prior to initiation or maintenance of therapy is less than 10 g/dL or the hematocrit is less than 30%.
- The starting dose is not greater than 450 units per kilogram (U/kg) per week or 40,000 units weekly.

Reduction of Allogeneic Red Blood Cell Transfusion in Members Undergoing Elective, Noncardiac, Nonvascular Surgery[1-3]

Authorization of 8 weeks may be granted for members scheduled to have an elective, noncardiac, nonvascular surgery when the pretreatment hemoglobin is greater than 10 to less than or equal to 13 g/dL.

Anemia Due to Zidovudine in HIV-Infected Members[1-3]

Authorization of 12 months may be granted for the treatment of anemia in HIV-infected members currently receiving zidovudine with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

Anemia Due to Myelodysplastic Syndrome[4,5,7,22,24]

Authorization of 12 weeks may be granted for the treatment of anemia due to myelodysplastic syndrome in members with pretreatment hemoglobin less than 10 g/dL or hematocrit less than 30%.

Anemia in Epidermolysis Bullosa[5,9]

Authorization of 12 weeks may be granted for the treatment of anemia in members with epidermolysis bullosa whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

Anemia in Congestive Heart Failure[5,25]

Authorization of 12 weeks may be granted for the treatment of anemia in congestive heart failure in members whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

Anemia due to Critical Illness[5,26]

Authorization of 12 weeks may be granted for the treatment of anemia due to critical illness in members whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

Anemia Due to Hepatitis C Treatment[5,10]

Authorization of 12 weeks may be granted for the treatment of anemia due to hepatitis C treatment in members who meet all of the following criteria:

- The member's hemoglobin is less than 10 g/dL or hematocrit is less than 30%.
- The member is receiving ribavirin in combination with either interferon alfa or peginterferon alfa.

Anemia in Porphyria Cutanea Tarda[5,20]

Authorization of 12 weeks may be granted for the treatment of anemia in members with porphyria cutanea tarda.

Anemia in Patients Who Will Not/Cannot Receive Blood Transfusions[5,11,12]

Authorization of 12 weeks may be granted for treatment of anemia in members who will not/cannot receive blood transfusions (e.g., religious beliefs) whose hemoglobin is less than 10 g/dL or whose hematocrit is less than 30%.

Prophylaxis of Anemia of Prematurity[5,21]

Authorization of 12 weeks may be granted for the prophylaxis of anemia of prematurity in members less than 1 year of age.

Iron Overload[5,15]

Authorization of 12 weeks may be granted for the treatment of iron overload in combination with phlebotomy.

Myelofibrosis-associated Anemia[4,5,7,13]

Authorization of 12 weeks may be granted for the treatment of myelofibrosis-associated anemia when both of the following criteria are met:

- The member has a hemoglobin level less than 10 g/dL or a hematocrit less than 30%.
- The member has an erythropoietin (EPO) level less than 500 mU/mL.

Anemia due to Radiation[5,14]

Authorization of 12 weeks may be granted for the treatment of anemia due to radiation.

Anemia During the Puerperium[5,16]

Authorization of 12 weeks may be granted for the treatment of anemia following childbirth.

Anemia due to Cancer[4,22]

Authorization of 12 weeks may be granted for the treatment of anemia in members who have cancer and are undergoing palliative treatment.

Blood Unit Collection for Autotransfusion[5,18,19]

Authorization of 12 weeks may be granted to increase the capacity for donation for future autologous transfusion prior to elective surgery.

Continuation of Therapy

Note: Requirements regarding current hemoglobin level exclude values due to a recent transfusion.

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Anemia Due to Concomitant Myelosuppressive Chemotherapy

Authorization of 12 weeks may be granted for the treatment of anemia due to concomitant myelosuppressive chemotherapy when all of the following criteria are met:

- The member is currently receiving therapy with epoetin alfa.
- The member does not have any exclusions listed in the Exclusions section.
- The member has experienced at least a 1 g/dL increase in hemoglobin or a 3% increase in hematocrit.
- The member's hemoglobin is less than 11 g/dL or the prescriber will hold or reduce the dose of epoetin alfa to maintain a hemoglobin level sufficient to avoid transfusion.
- Treatment will not extend beyond 8 weeks following the final dose of myelosuppressive chemotherapy given in the member's current chemotherapy regimen.

Anemia Due to Zidovudine in HIV-Infected Members

Authorization of 12 months may be granted for the treatment of anemia due to zidovudine in HIV-infected members when both of the following criteria are met:

- The member is currently receiving therapy with epoetin alfa.
- Epoetin alfa has been effective for treating the diagnosis or condition.

Reduction of Allogeneic Red Blood Cell Transfusion in Members Undergoing Elective, Noncardiac, Nonvascular Surgery

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

All Other Indications

Authorization of 12 Weeks may be granted for all other indications when all of the following criteria are met:

- The member is currently receiving therapy with epoetin alfa.
- The member is receiving epoetin alfa for an indication listed in the Coverage Criteria section.
- Epoetin alfa has been effective for treating the diagnosis or condition.

Summary of Evidence

The contents of this policy were created after examining the following resources:

- The prescribing information for Epogen, Procrit and Retacrit.
- The available compendium
    - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    - Micromedex DrugDex
    - American Hospital Formulary Service-Drug Information (AHFS-DI)
    - Lexi-Drugs

    - Clinical Pharmacology
- Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for Anemia in Chronic Kidney Disease
- Management of Cancer-Associated Anemia with Erythropoiesis-Stimulating Agents: American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) Clinical Practice Guideline Update
- NCCN Guideline: Myelodysplastic syndromes
- NCCN Guideline: Myeloproliferative neoplasms
- NCCN Guideline: Hematopoietic growth factors
- Medicare National Coverage Determinations (NCD) Manual

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Epogen, Procrit and Retacrit are covered in addition to the following:

- Anemia in members with myelodysplastic syndromes (MDS)
- Anemia in epidermolysis bullosa
- Anemia in congestive heart failure
- Anemia due to critical illness
- Anemia due to hepatitis C treatment with ribavirin in combination with either interferon alfa or peginterferon alfa
- Anemia in porphyria cutanea tarda
- Anemia in patients who will not/cannot receive blood transfusions
- Prophylaxis of anemia of prematurity
- Iron overload
- Myelofibrosis-associated anemia
- Anemia due to radiation
- Anemia due to puerperium
- Cancer patients who are undergoing palliative treatment
- Blood unit collection for autotransfusion

Explanation of Rationale

Support for FDA-approved indications (anemia due to chronic kidney disease, anemia due to zidovudine, anemia due to chemotherapy in members with cancer, reduction of allogenic RBC transfusions in members undergoing elective, noncardiac, nonvascular surgery) can be found in the manufacturer's prescribing information.

Support for using epoetin alfa to treat anemia due to myelodysplastic syndrome can be found in the National Comprehensive Cancer Network's (NCCN) guideline for myelodysplastic syndromes. The NCCN Guideline for myelodysplastic syndrome supports the use of epoetin alfa for the treatment of symptomatic anemia associated with lower risk (IPSS low/intermediate-1) disease with del(5q), with or without one other cytogenetic abnormality (except those involving chromosome 7). Epoetin alfa can also be used for the treatment of symptomatic anemia associated with lower risk (IPSS-R very low/low/intermediate) disease with no del(5q), with or without other cytogenic abnormalities with ring sideroblasts < 15% (or ring sideroblasts < 5% with an SF3B1 mutation), with serum erythropoietin (EPO) $\leq$ 500 mU/mL as either a single agent, or in combination with either lenalidomide or granulocyte-colony stimulating factor (G-CSF) following no response or erythroid response followed by loss of response to an erythropoiesis-stimulating agent (ESA) alone. Finally, epoetin alfa can be used as treatment of symptomatic anemia associated with lower risk (IPSS-R

very low/low/intermediate) disease with no del(5q), with or without other cytogenic abnormalities with ring sideroblasts ≥ 15% (or ring sideroblasts ≥5% with an SF3B1 mutation), with serum EPO ≤ 500 mU/mL as a single agent or in combination with a G-CSF.

Support for using epoetin alfa to treat anemia associated with epidermolysis bullosa with concurrent intravenous iron can be found in a case report. Fridge and Vichinsky (1998) reported 4 of 5 children with epidermolysis bullosa and severe refractory anemia became transfusion-independent after treatment with erythropoietin and intravenous iron. Iron 10 to 20 milligrams (mg)/kilogram (kg) as iron dextran was administered monthly and erythropoietin was given in escalating doses of 150 to 350 units/kg 3 times per week. Another patient whose pretreatment erythropoietin level was high was treated with intravenous iron alone. All patients responded. Mean hemoglobin rose from 6.8 to 10.0 grams/deciliter (p=0.01) and hematocrit from 23.8% to 33.1% (p=0.03). One patient died of sepsis; the other 4 continue to receive treatment and have reported an improved quality of life, accelerated wound healing, and improvement in weight-for-height percentile.

Support for using epoetin alfa to treat anemia in patients with congestive heart failure can be found in a Cochrane review. Ngo, Kotecha, Walters, et al (2010) reported that in 794 adults with symptomatic congestive heart failure (CHF) and mild anemia, treatment with erythropoietin stimulating agents (ESAs; including darbepoetin alfa, epoetin alfa, and epoetin beta with or without iron) improved exercise tolerance (7 studies; n=623) compared with placebo or no treatment, including exercise duration (4 studies, n=362; +96.82 seconds [95% CI, 5.22 to 188.42]), distance on the 6 minute walk test (4 studies, n=261; +69.33 meters [95% CI, 16.99 to 121.67]), and peak VO2 (3 studies, n=102; +2.29 mL/kg/min [95% CI, 0.62 to 2.95]). Hemoglobin was significantly increased in patients receiving ESAs (11 studies, n=782; +1.98 g/dL [95% CI, 1.62 to 2.35]), as well as a significant improvement in New York Heart Association (NYHA) class (8 studies, n=657; -0.73 points) and some quality of life scores. Left ventricular ejection fraction (LVEF) improved by 5.77% (5 studies, n=321) with ESAs, and BNP (5 studies, n=203) decreased by 226.99 picograms (pg)/mL compared with placebo or no treatment; hospitalizations related to CHF and all-cause mortality were also significantly reduced with ESA use.

Support for using epoetin alfa to treat anemia due to critical illness can be found in a prospective, randomized, double-blind, placebo-controlled trial of 1302 adult ICU patients by Corwin et al. (2002). Patients aged 18 years or older who were admitted to a medical, surgical, or medical/surgical ICU for 3 days and had a hematocrit (HCT) of less than 38% were randomized to receive either epoetin alfa 40,000 units (n=650) or placebo (n=652) subcutaneously on ICU day 3. In patients who remained hospitalized, study drug was continued once weekly for a total of 3 doses (study days 1, 7, and 14), and a fourth dose was administered to patients remaining in the ICU on day 21. Epoetin alfa was held if the HCT was 38% or higher prior to the scheduled administration. All patients received 150 milligrams/day or more of elemental iron either orally or via nasogastric tube starting on study day 1, and patients with an inadequate response to oral iron were given parenteral iron. Unless clinically warranted at higher values, RBC transfusions discouraged until the HCT fell below 27% or the Hb level was less than 9 grams/deciliter (g/dL). At baseline, the mean Hb level was 9.97 g/dL for both groups. Results showed that the percentage of patients who received any RBC transfusion during the 28-day follow-up period (primary efficacy endpoint) was significantly lower in the epoetin alfa group (50.5%; n=328/650) compared to placebo (60.4%; n=394/652) (p less than 0.001; odds ratio (OR), 0.67; 95% confidence interval (CI), 0.54 to 0.83). Treatment difference between groups, based on time to first transfusion or the composite endpoint of time to first transfusion or death (secondary endpoint), was evident by study day 7 and increased progressively during the 28-day follow-up period. Among other secondary endpoints the median number of total RBC units transfused per patient was 1 (interquartile range (IQR), 0 to 3) and 2 (IQR, 0 to 4) for the epoetin alfa and placebo groups, respectively (p less than 0.001). The ratio of RBC transfusion rate per number of days alive was 0.81 (95% confidence interval (CI), 0.79 to 0.83), yielding a 19% relative reduction in transfusion burden for the epoetin alfa group compared to placebo. The mean Hb increase from baseline was significantly greater for epoetin alfa-treated patients (1.32 g/dL) compared to placebo-treated patients

(0.94 g/dL; p less than 0.001). Subgroup analyses based on admitting diagnosis, age (older or younger than 55 years), or APACHE scores (lower or higher than 20) yielded consistent results for the primary efficacy endpoint. The median length of hospitalization, ICU-free days, and ventilator-free days were similar between groups. There were no statistically significant differences in mortality or serious adverse events between the groups.

Support for using epoetin alfa to treat anemia due to combination therapy of ribavirin and interferon alfa or ribavirin and peginterferon alfa can be found in a prospective, double-blind, placebo-controlled trial of 185 patients by Afdhal et al. (2004). Patients (n=185) with hemoglobin (Hb) of 12 grams/deciliter (g/dL) or less who were receiving any combination of ribavirin and interferon alfa for chronic hepatitis C virus (HCV) infection were randomized to receive epoetin alfa (Procrit(R)) 40,000 units subcutaneously once weekly (n=93) or placebo (n=92) for 8 weeks. If a patient's Hb level had not increased by at least 1 g/dL after 4 weeks of treatment, the dose was increased to 60,000 units once weekly. At the end of the 8-week double-blind period, patients were eligible for enrollment to an open-label modified crossover phase if they were receiving epoetin alfa in the double-blind phase and had a Hb increase of at least 1 g/dL, or if they were receiving placebo in the double-blind phase and ended that phase with Hb of 12 g/dL or less or had a ribavirin dose reduction due to anemia. The primary endpoint was ribavirin dose maintenance at the end of the 8-week double-blind phase. Patients had been on HCV treatment for an average of 12 and 14 weeks in the epoetin alfa and placebo groups, respectively, at the time of randomization. Ribavirin dose was maintained in 88% of patients who received epoetin alfa compared to 60% of patients who received placebo (p less than 0.001). In addition, the ribavirin dose stayed the same or increased since the start of HCV therapy in 77% of patients on epoetin alfa and 46% of patients on placebo (p less than 0.001). Patients who received epoetin alfa in the double-blind phase and continued receiving it in the open-label phase maintained their mean ribavirin dose throughout the open-label phase. Patients who received placebo in the double-blind phase had a significant increase in their mean ribavirin dose after receiving epoetin alfa in the open-label phase (p less than 0.001). Hemoglobin significantly improved in the epoetin alfa group (10.8 +/0.8 g/dL to 13 +/1.3 g/dL) compared to the placebo group (10.8 +/- 1 g/dL to 10.9 +/- 1.1 g/dL) in the double-blind phase (p less than 0.001). Quality of life significantly improved in patients who received epoetin alfa compared to those who received placebo in the double-blind phase, as assessed with a linear analog scale assessment (LASA) and the Medical Outcomes Short Survey Form-36 (version 2). One case of cerebral thrombosis occurred that was possibly related to epoetin alfa. No differences in liver function or HCV viral loads were detected.

Support for using epoetin alfa to treat anemia in porphyria cutanea tarda can be found in a case report. Anderson et al. (1990) reported a woman with life threatening porphyria cutanea tarda associated hemodialysis achieved remission of the porphyria after initiation of erythropoietin therapy 150 units/kilogram. Plasma porphyrin levels decreased from 211 mcg/dl (normal less than 2 mcg/dl) to less than 10% of this level after four months of erythropoietin therapy and intermittent phlebotomy.

Support for using epoetin alfa to treat anemia in patients who will not/cannot receive blood transfusions is supported by several small studies. Atabek and colleagues (1995) studied twenty Jehovah’s Witness patients with post-surgical hematocrits below 25% treated with erythropoietin (plus standard iron and nutritional support), compared to 20 retrospective control patients maintained with iron and nutritional support alone. The patients receiving erythropoietin demonstrated a more rapid rise in hematocrit, particularly within the first week, which was sustained after two weeks. Thirteen patients received erythropoietin as 300 units/kg intravenously (IV) 3 times weekly for the first week, then 150 units/kg 3 times weekly during the second week; seven patients received 100 units/kg IV 3 times weekly for 2 weeks. Among all erythropoietin-treated patients, the mean hematocrit rose from 15.8% to 19.3% after one week, and to 22.5% after two weeks. Control patients demonstrated an initial fall from 12.8% to 12.5% at the end of one week, rising to 17.8% after two weeks. Results reached statistical significance only at the end of the first week.

Four Jehovah's Witness patients who either exhibited preoperative anemia or developed postoperative anemia refractory to endogenous erythropoietin were discharged from the hospital in good condition after treatment with recombinant human erythropoietin (EPO) 50 to 280 units per kilogram body weight daily. The fifth patient, who exhibited no signs of systemic inflammation following emergency hemicolectomy, was also treated with intravenous iron, but not with erythropoietin. No predictor of response was identified in this series; therefore, use of erythropoietin in this patient subgroup would be based strictly on humanitarian grounds (Wolff et al., 1997).

The NCCN Guideline for hematopoietic growth factors supports the use of epoetin alfa for anemia in select patients who refuse blood transfusions due to religious beliefs or personal preferences.

Support for using epoetin alfa as prophylaxis against anemia associated with prematurity is supported by a randomized, placebo-controlled trial by Donato and colleagues (2000). One hundred and fourteen low-birth-weight infants (less than 1250 g) who received erythropoietin within 72 hours of birth saw improved hematocrit and reticulocyte counts compared to later initiation (2 weeks after birth), but it failed to affect overall transfusion requirements. Intravenous (IV) erythropoietin dosing was 1250 units/kg/week as 5 divided doses, along with oral iron and folic acid supplementation. The percentage of patients requiring transfusions, the number of transfusions per patient, and total phlebotomy losses did not differ statistically between the 2 study groups. A post hoc subgroup analysis determined that total per-patient transfusion requirements were significantly lower with early versus late erythropoietin initiation (3.4 vs 5.4) in infants with birth weight under 800 g and phlebotomy losses greater than 30 mL/kg.

Support for using epoetin alfa to treat iron overload in combination with phlebotomy is found in a small study by McCarthy et al. (1989). Five transfusion dependent hemodialysis patients suffering from iron overload were treated with erythropoietin (150 units/kilogram) and phlebotomy in an attempt to reduce iron stores and maintain a hematocrit of 25%. During the 18-week study period, total iron removal ranged from 732 to 2797 milligrams and mean serum ferritin decreased from 3189 +/- 1076 micrograms/liter (mcg/L) to 1676 +/- 342 mcg/L.

Support for using epoetin alfa to treat myelofibrosis-associated anemia can be found in the National Comprehensive Cancer Network’s guideline for myeloproliferative neoplasms. The NCCN Guideline supports the use of epoetin alfa for the management of myelofibrosis-associated anemia with serum erythropoietin (EPO) less than 500 mU/mL.

In a small, open-label study by Cervantes and colleagues (2004), treatment with human recombinant erythropoietin (EPO) improved anemia in some patients with myelofibrosis. Patients (n=20; median age, 64.5 years (yr); range, 45-91 yr; median baseline hemoglobin (Hb) level, 8.9 grams/deciliter (g/dL); range, 7.7-10 g/dL; median baseline erythropoietin level, 81 units/liter (L); range, 8-282 units/L; baseline erythropoietin level less than 125 units/L, n=16) having myelofibrosis with myeloid metaplasia and anemia who were red blood cell (RBC) transfusion dependent (n=13) or had a Hb level of 10 g/dL or less initially received subcutaneous erythropoietin 10,000 units 3 days per week. Erythropoietin was increased to 20,000 units 3 days per week if a response was not obtained after 2 months and erythropoietin was discontinued in patients who did not experience a response at 3 months. Patients received RBC transfusions for overtly symptomatic anemia or Hb levels less than 8 g/dL; additionally, patients with inadequate iron status received oral iron supplements (100 milligrams/day). Most patients in this study (n=17) had received one or more prior therapies (hydroxyurea, n=11; danazol, n=10; anagrelide, n=4; splenectomy, n=3; interferon alfa, n=1; prednisone, n=1; reduced-intensity conditioning allogeneic stem-cell transplantation, n=1) which were discontinued prior to study enrollment due to lack of or inadequate response. Nine patients (45%) had a good response to erythropoietin therapy, with 4 patients (20%) experiencing a complete response (defined as no RBC transfusion requirements with normalization of Hb) and 5 patients (25%) experiencing a partial response (defined as a 50% or greater reduction in monthly RBC transfusions and a Hb level of greater than 10 g/dL for at least 8 weeks). Additionally, at a median follow-up of 12.5 months (range, 4-21 months), 4 patients (20%) continued to have a response. Lack of a RBC transfusion requirement and a higher baseline Hb

level correlated with a favorable response in a univariate analysis. Overall, erythropoietin therapy was well tolerated; although, increased splenomegaly was reported in 2 patients.

Support for using epoetin alfa to treat anemia due to radiation therapy is supported by a study by Sweeney et al. (1998). In a randomized, open-label Phase II study of 48 patients with carcinoma of the lung, uterine cervix, prostate or breast with associated anemia, epoetin alfa 200 units/kilogram/day for 5 consecutive days per week for up to 7 weeks during radiotherapy significantly increased hemoglobin levels as compared to a control group. The average pre- and post-radiotherapy hemoglobin values were 12.1 and 13.6 grams/deciliter (g/dL) in the erythropoietin group as compared to 10.7 and 11 g/dL in the control group (p = 0.001). This translates to a weekly mean increase of 0.4 g/dL with epoetin alfa. Overall, 42% and 0% of the active and control groups, respectively, achieved the target hemoglobin level (15 g/dL in men, 14 g/dL in women). Epoetin alfa somewhat attenuated the radiotherapy-induced decline in platelet counts. No between-group differences occurred with respect to quality-of-life scores or adverse effects. Further study is needed to determine the effect of epoetin alfa on clinically significant endpoints.

Support for using epoetin alfa to treat anemia during the puerperium is supported by a randomized, placebo-controlled trial (n=60) conducted by Breymann and colleagues (2000). The combination of intravenous (IV) erythropoietin (EPO) 300 units/kilogram/day plus IV iron sucrose 200 milligrams (mg)/day on days 1 to 4 postpartum was more effective than IV iron alone or oral elemental iron sulfate 80 mg plus folic acid 0.35 mg twice daily in the treatment of postpartum anemia (hemoglobin less than 10 grams/deciliter). Subjects had lost an average of 806 milliliters of blood during delivery. On day 7, the reticulocyte count and increase in hemoglobin and hematocrit were significantly higher in the erythropoietin-iron group than either comparator group. As of day 14, erythropoietin recipients experienced an average 11.3% rise in hematocrit from baseline, significantly greater than iron alone. Transfusions were avoided in all three groups. No serious adverse effects occurred in any participant.

Support for using epoetin alfa to treat anemia in patients who have cancer and are undergoing palliative treatment can be found in the National Comprehensive Cancer Network's guideline for hematopoietic growth factors.

Support for using epoetin alfa to increase the capacity for donation for future autologous transfusion prior to elective surgery is supported by several studies. Evidence supports the use of epoetin to prevent anemia in patients who donate blood and to increase the capacity for donation (for future autologous transfusion) prior to elective surgery. The medication has been found to be effective in females, patients with low packed-cell volumes due to anemia or small body size, and patients requiring donation of 4 units or more of blood. Preoperative autologous blood donation with erythropoietin support was beneficial in two studies of abdominal aortic aneurysm (AAA) repair. In a consecutive series (n=20), intravenous erythropoietin 6000 units was administered immediately after withdrawal of one unit of blood (14 days prior to surgery) and again 3 days later, then repeated with the second autologous donation 1 week later (1 week prior to surgery). Subjects also received iron supplementation. The systolic blood pressure decreased to 119 millimeters of mercury following the two blood donations, with no instances of hypertension reported. From before the first blood donation to the time of surgery, hemoglobin declined from 13.8 to 12.4 grams/deciliter, while the reticulocyte count rose significantly. Endogenous erythropoietin levels remained unaffected. While all patients received perioperative autologous transfusions of one to two units, only two patients needed a homologous blood transfusion (Urayama et al., 2000).

In a study of 47 patients by Goodnough et al. (1989), the mean number of units of blood collected per patient in the erythropoietin group was 5.4 +/- 0.2 compared with 4.1 +/- 0.2 in the placebo group. These patients received either erythropoietin in doses of 600 units/kilogram twice weekly for three weeks prior to surgery or placebo. Patients were excluded if their hematocrits fell below 34%. Of the patients treated with erythropoietin (n=23) only 4% were unable to donate more than 4 units of blood whereas 29% of those patients receiving placebo (n=24) were unable to donate the same number of units.

Use in cancer and related neoplastic conditions is covered according to the conditions outlined in National Coverage Determination Manual section 110.21 (Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions).

References

1. Epogen [package insert]. Thousand Oaks, CA: Amgen Inc.; April 2024.
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