PROCRIT® (epoetin alfa)
Flexible Weekly Dosing - Use in Anemia due to Chemotherapy in Patients with Cancer

SUMMARY

- PROCRIT is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy (CT), and upon initiation, there is a minimum of two additional months of planned CT.[1]
- Initiate PROCRIT in patients on cancer CT only if the hemoglobin (Hb) is less than 10 g/dL, and if there is a minimum of two additional months of planned CT.[1]
- Use the lowest dose of PROCRIT necessary to avoid red blood cell (RBC) transfusions. [1]
- Extended/alternative dosing has been studied in the following scenarios:
  - Initiation: higher once weekly (QW) dosing[2]
  - Initiation/Maintenance: QW followed by every other week (Q2W) dosing[3,4]
  - Initiation/Maintenance: QW followed by once every 3 weeks (Q3W) dosing[5]
- Smaller prospective studies (N≤50) have investigated the use of epoetin alfa (EPO) 60,000 Units (U) QW[6] and EPO 60,000 U QW followed by 120,000 U Q3W.[7]
- An additional article identified as relevant in the published literature is cited here.[8]

BACKGROUND

Various studies evaluating extended or alternative dosing regimens of EPO have been conducted in cancer patients with anemia receiving myelosuppressive-CT as well as in anemic cancer patients not receiving CT or radiation therapy. Extended/alternative dosing regimens of EPO may potentially offer added convenience to both health care providers and the patient.[9]

PRODUCT LABELING

- Initiate PROCRIT in patients on cancer CT only if the Hb is less than 10 g/dL, and if there is a minimum of two additional months of planned CT.[1]
- Use the lowest dose of PROCRIT necessary to avoid RBC transfusions.[1]

Recommended Starting Dose[1]

Adults:

- 150 U/kg subcutaneously (SC) 3 times per week until completion of a CT course or
- 40,000 U SC QW until completion of a CT course.

Pediatric Patients (5 to 18 years):

- 600 U/kg intravenously QW until completion of a CT course.

Dose Reduction[1]

Reduce dose by 25% if:

- Hb increases greater than 1 g/dL in any 2-week period or
- Hb reaches a level needed to avoid RBC transfusion.
- Withhold dose if Hb exceeds a level needed to avoid RBC transfusion. Reinitiate at a dose 25% below the previous dose when Hb approaches a level where RBC transfusions may be required.

Dose Increase[1]

- After the initial 4 weeks of PROCRIT therapy, if Hb increases by less than 1 g/dL and remains below 10 g/dL, increase dose to:
  - 300 U/kg three times per week in adults or
  - 60,000 U QW in adults
  - 900 U/kg (maximum 60,000 U) QW in pediatric patients
- After 8 weeks of therapy, if there is no response as measured by Hb levels or if RBC transfusions are still required, discontinue PROCRIT.

CLINICAL DATA

Initiation: Higher QW Dosing

EPO 80,000 U QW

Waltzman et al (2005)[2] evaluated the hematologic response, clinical outcomes, and safety of EPO in treating anemia in patients with cancer receiving CT (N=69).

Study Design/Methods

- This was a non-randomized, open-label, multicenter, pilot study.
- Patients with non-myeloid malignancies and Hb ≤11 g/dL who were scheduled to receive ≥12 weeks of CT received EPO 80,000 U SC QW for up to 12 weeks.
- If the Hb level rose to >13 g/dL, then EPO was held until Hb ≤12 g/dL, and the dose was reduced to 60,000 U SC QW.
- EPO dose was also reduced if Hb levels increased >1.3 g/dL in a 2-week period.
- Ferrous sulfate 325 mg per day was administered as iron supplementation if tolerated and not contraindicated.
- **The primary endpoint** was the proportion of patients that had a major hematologic response, defined as an increase in Hb ≥2 g/dL from baseline or a Hb ≥12 g/dL at any time, independent of transfusions within the previous 28 days.

Results

Patient Characteristics

- The mean baseline Hb was 10.1 g/dL.

Efficacy

- In the modified intent-to-treat (mITT) population (n=68), mean EPO dose at week 6 was 71,300 U but decreased to 65,800 U by week 12.
- Accounting for held or missing doses, mean EPO U/week were approximately 62,700 U.
- By the end of the study, 72% (n=49) of patients experienced major response and 19% (n=13) experienced minor response.
- The mean time to first major response was 6.7 weeks; the final mean Hb was 12.3 g/dL.
- The mean Hb change from baseline was 1.2 g/dL at 4 weeks, 1.9 g/dL at 8 weeks, and 2.2 g/dL at 12 weeks.
- A total of 6 (9%) patients received ≥1 packed red blood cell (PRBC) transfusions over the course of the study:
  - Between days 1 and 28, 4 patients received ≥1 PRBC transfusion; the mean number of U per transfusion was 2.2 U.
  - After day 28, 2 patients received ≥1 PRBC transfusion; the mean number of U per transfusion was 2 U.

Safety

- A total of 48 patients (69.6%) had ≥1 dose reduction or hold because of Hb >13 g/dL, Hb increase >1.3 g/dL in a 2-week period, or missed visits.
- Overall, 6 patients discontinued the study due to adverse events (AEs), of which 4 patients expired within 15 days of the last dose.
- One patient died during 30-day follow-up. No deaths were considered related to study drug.

Initiation/Maintenance: QW Followed by Q2W

EPO 60,000 U QW Followed by 60,000 U Q2W

Gregory et al (2007)[3] evaluated the efficacy and safety of an initial EPO regimen of 60,000 U QW followed by a maintenance dosing regimen of EPO 60,000 U Q2W in treating anemia in patients with cancer receiving CT for at least 16 weeks (N=129).

Study Design/Methods

- This was an open-label, multicenter study.
- Patients had a Hb ≤11 g/dL and were scheduled to receive CT for a non-myeloid malignancy, either weekly or monthly, for ≥16 weeks.
- The study consisted of 2 treatment phases.
  - During the initiation-dosing phase (IDP), patients received EPO 60,000 U SC QW to achieve a target Hb of 12 g/dL (maximum duration of 12 weeks).
  - During the extended-dosing phase (EDP), patients who achieved a Hb target of 12 g/dL in the IDP were administered EPO 60,000 U SC Q2W to maintain Hb between 11.0 g/dL and 12.5 g/dL.
- The EPO dose was withheld if Hb >13 g/dL, and the dose was reduced if the rate of Hb rise was >1.3 g/dL in a 2-week period.
- Ferrous sulfate 325 mg/day was administered as tolerated.
- The maximum study duration (IDP + EDP) was 24 weeks.
- **The primary endpoint** was the proportion of patients who achieved a hematopoietic response during the IDP, defined as an Hb increase ≥2 g/dL from baseline, or achievement of a Hb level ≥12 g/dL.
- Several **secondary endpoints** were evaluated.

Results

Patient Characteristics

- The mean baseline Hb was 10.0±0.9 g/dL.

Efficacy

- Among 45 (34.9%) of patients who only completed IDP, the average time spent in IDP was 5.2 weeks and the mean weekly EPO dose was 59,020 U.
  - A total of 6% and 11% of patients had ≥1 dose withheld or reduced, respectively. A total of 68% (84/124) of patients had a hematopoietic response.
  - The median time to achieve a hematopoietic response was 30 days (95% confidence interval: 29–37).
  - A total of 11.3% (14/124) of patients had a Hb increase from baseline of 1 g/dL to 1.9 g/dL.
  - A total of 14% (18/129) of patients received 24 PRBC transfusions (mean, 2.6 U per transfused patient).

- Among 84 patients (68%) who achieved a hematopoietic response and proceeded to the EDP, the mean treatment duration in the EDP phase was 13.2 weeks and the mean EPO Q2W dose was 49,515 U.
  - A total of 61% (51/84) of patients maintained a mean Hb between 11.0 g/dL and 12.5 g/dL.
  - A total of 70.2% (59/84) of patients withdrew early from the EDP, of which 16 patients withdrew due to Hb decrease to <11 g/dL.
  - A total of 63% and 56% of patients required ≥1 dose of EPO withheld or reduced, respectively.
  - The mean Hb level at start of EDP was 12.4±0.35 g/dL.
  - The mean Hb level of individual patients in the EDP was 12.3±0.62 g/dL.
  - A total of 88% (74/84) of patients maintained a mean Hb between 11.0 g/dL and 13.0 g/dL up to the time of withdrawal or study end.
  - The proportion of patients with Hb levels in this range by study week ranged from 69.6% to 97.5%.
  - No patient received a transfusion during the EDP.

Safety

- The most common AEs were nausea (28.7%), fatigue (20.9%), and vomiting (17.8%).
- Serious adverse events (SAEs) were reported in 50.4% (n=65) of patients.
- The most common reported SAEs included disease progression (6.2%), dehydration (3.9%), and vomiting (3.9%).
- During the study or within 30 days after last dose, 15 (11.6%) patients died.
- A total of 11.6% (n=15) of patients experienced clinically relevant thrombotic vascular events (CRTVEs).
- During the IDP, 4.7% (6/129) of patients had 7 CRTVEs, including deep vein thrombosis (DVT; 4 occurrences), pulmonary embolism (1 occurrence), subclavian vein thrombosis (1 occurrence), and venous thrombosis (1 occurrence).
- During the EDP: 9.5% (8/84) had 9 CRTVEs, including DVT (3 occurrences), hemiparesis (2 occurrences), myocardial infarction (1 occurrence), myocardial ischemia (1 occurrence), portal vein thrombosis (1 occurrence), and transient ischemic attack (1 occurrence).
- All CRTVEs were considered unrelated to study drug, except the portal vein thrombosis which was considered possibly related.
- A Hb increase ≥1 g/dL within a 2-week period was observed in 12 of 14 patients (85.7%) who had a CRTVE sometime during their study participation.
- More than 1 Hb level >13 g/dL was observed in 7 of 14 patients (50%) who had a CRTVE.

Reddy et al (2006)[4] evaluated the efficacy and safety of initial administration of EPO 60,000 U QW for 4 weeks followed by EPO 60,000 U Q2W extended dosing regimen in treating anemia in patients with cancer undergoing CT (N=51).

Study Design/Methods

- This was an open-label, multicenter, single-arm pilot study.
- Patients had a Hb ≤11 g/dL and were scheduled to receive CT for a non-myeloid malignancy, either weekly or monthly, for ≥16 weeks.
- The study consisted of 2 treatment phases: an IDP, when patients were administered EPO 60,000 U SC QW for 4 weeks, followed by an EDP, when EPO 60,000 U SC Q2W was initiated at week 5 and continued for up to an additional 12 weeks.

- EPO treatment was withheld when Hb levels were >13 g/dL and resumed at 40,000 U when Hb was ≤12 g/dL.
- If Hb increase was <1 g/dL during the IDP or Hb decreased ≥2 g/dL during the EDP, patients were withdrawn from the study.
- Oral ferrous sulfate 325 mg daily or an equivalent preparation was administered to all patients as tolerated.
- Transfusions were given if deemed medically necessary by the investigator.
- **The primary endpoint** was the proportion of patients achieving a hematological response, defined as ≥1 g/dL Hb increase from baseline at anytime during the IDP (up to week 5).
- **Secondary endpoints** and additional outcome measures were evaluated.

Results

Patient Characteristics

- The mean baseline Hb was 10.1 g/dL±0.79 g/dL.

Efficacy

- During the IDP (n=51), 19.6% (n=10) of patients had ≥1 dose of EPO withheld for Hb >13 g/dL and 23.5% (n=12) of patients had ≥1 EPO dose reduction after a dose was withheld for Hb >13 g/dL or for a Hb rate increase >1.3 g/dL in a 2-week period.
  - The mean EPO dose was 58,268 U weekly.
  - A total of 64.7% (n=33) of patients achieved a hematological response.
  - The mean time to hematological response was 15.5±6.7 days.
- Of the patients included in the IDP, 56.9% (n=29) of patients advanced to the EDP.
  - A total of 69% (n=20) of patients had ≥1 dose withheld for Hb >13 g/dL.
  - A total of 69% (n=20) of patients had ≥1 EPO dose reduction after a dose was withheld for Hb >13 g/dL or for a Hb rate increase >1.3 g/dL in a 2-week period.
  - The mean EPO dose was 45,790 U Q2W.
  - The mean Hb level at the start of week 5 was 12.4 g/dL±0.99 g/dL.
  - A total of 41.4% (n=12) of the patients exhibited a further Hb increase.
    - A total of 6.9% (n=2) of patients had an average Hb ≥1 g/dL greater than Week 5 Hb value.
    - A total of 34.5% (n=10) of patients had an EDP average Hb 0–0.9 g/dL higher than Week 5 Hb value.
  - Overall, 17 patients did not experience a further Hb increase. Hb decreased by a mean of -1 g/dL±0.6 g/dL.
  - A total of 17.2% (n=5) of patients withdrew from the study due to a Hb decrease ≥2 g/dL.
  - The mean final Hb value was 11.7 g/dL±1.28 g/dL in the 29 patients in this phase.
- During both phases, the mean Hb level increased by 2 g/dL from baseline by week 6 and then remained stable for rest of study.
  - Four patients received 5 transfusions (weeks 1–4: n=3; weeks 5–8: n=1; weeks 9–12: n=1).

Safety

- One or more AEs were reported in 94.1% of patients. Most AEs were considered to be not related to study drug.
- The most commonly reported AEs included nausea (23.5%), asthenia (21.6%), and fatigue (21.6%).
- Overall, ≥1 SAE was reported in 25.5% (n=13) of patients.

- CRTVEs were reported in 2 patients (3.9%) who each experienced 1 CRTVE during the IDP of weekly dosing. One patient experienced DVT, and the other patient experienced chest pain. Both thrombotic vascular events were not related to study drug.
- Three (5.9%) patients died during the study due to disease progression (n=2) or sepsis (n=1).

Initiation/Maintenance: QW Followed by Q3W

EPO 60,000 U QW Followed by 80,000 U Q3W

Montoya et al (2007)[5] evaluated the safety and efficacy of EPO at a starting dose of 60,000 U QW followed by maintenance doses of 80,000 U Q3W in patients with CT-induced anemia (N=115).

Study Design/Methods

- This was a prospective, open-label, single-arm, multicenter study that included patients with non-myeloid malignancy, Hb ≤11 g/dL, and scheduled to receive CT Q3W.
- There were 2 treatment phases: an IDP when EPO was administered as 60,000 U SC QW for up to 12 weeks until a target Hb of 12 g/dL was achieved and an EDP when EPO was administered as 80,000 U SC Q3W at the beginning of the next CT cycle.
- Patients were withdrawn from the study if they did not achieve a Hb of 12 g/dL in the IDP or if Hb decreased <11 g/dL in the EDP.
- For either phase, EPO was withheld if Hb >13 g/dL and was resumed at a reduced dose (40,000 U SC QW during the IDP and 60,000 SC Q3W during the EDP) when Hb decreased to ≤12 g/dL. The dose was reduced similarly if Hb increased >1.3 g/dL in any 2-week period.
- Oral ferrous sulfate 325 mg was administered to all patients as needed and as tolerated.
- The maximum study duration was 24 weeks for both phases.
- **The primary efficacy endpoint** was the proportion of patients achieving hematopoietic response, defined as Hb increase from baseline ≥2 g/dL or Hb ≥12 g/dL during IDP.

Results

Patient Characteristics

- Mean baseline Hb was 10.2±0.84 g/dL.

Efficacy

- In the IDP, among evaluable patients, hematopoietic response was achieved in 76.4% (84/110) of patients.
  - A total of 5.5% of patients achieved a ≥1.0 to ≤1.9 g/dL rise in Hb from baseline.
  - A total of 17/115 patients received blood transfusions.
- The mean Hb level at start of the EDP was 12.3±0.62 g/dL and the mean Hb level during this phase was 12.0±0.72 g/dL.
  - A total of 87.7% of patients maintained average Hb between >11.0 g/dL and ≤13.0 g/dL and 74.0% maintained average Hb between >11.0 g/dL and ≤12.5 g/dL.
  - A total of 2/73 patients received blood transfusions.

Safety

- The most common reported AEs included: nausea (38.3%), fatigue (32.2%), neutropenia (25.2%), vomiting (22.6%), and diarrhea (20.9%).
- Grade 3 and grade 3/4 neutropenia were reported in 6 and 13 patients, respectively.

- SAEs were reported in 44.3% (n=51) of patients; the most commonly SAEs reported included: dehydration (7%), febrile neutropenia (6.1%), and pyrexia (6.1%).
- CRTVEs were experienced by 7.8% (n=9) of patients in the IDP and none during the EDP; none of the thrombotic vascular events were considered related to study drug.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 03 September 2024. To streamline this document and present the most relevant information, only prospective studies with >50 patients are summarized above. Smaller prospective studies (N≤50) are cited in the Summary section.

REFERENCES

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