

# Erythropoietin In Anemia of Chemotherapy

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## Summary

Concerns about the risk of decreased survival and increased thromboembolism with erythropoiesis stimulating agents have developed in recent years. Updated guidelines for the use of these agents in cancer and new black box warnings have occurred as a result of these concerns. The guidelines note that the available agents have similar efficacy and that evolving information about risks must be considered.

## Key Points

- Anemia affects 13 to 80 percent of patients undergoing treatment for solid tumors.
- Epoetin alpha and darbepoetin are equally effective erythropoiesis stimulating agents.
- Darbepoetin can be given at longer intervals because of its longer half-life.
- Although fraught with design problems, several recently published studies show a higher mortality, a higher number of thrombotic events, and an increase in local recurrences in patients with head and neck cancer with erythropoiesis stimulating agents.
- Updated clinical practice guidelines on the use of epoetin and darbepoetin in cancer patients are available.
- To minimize the risk of adverse events, the target hemoglobin should be 12 g/dL or less when these agents are used in chemotherapy-induced anemia.
- These agents should not be used to treat anemia associated with malignancy among patients with either solid or non-myeloid hematological malignancies that are not receiving concurrent chemotherapy.

ERYTHROPOIESIS STIMULATING AGENTS (ESAs) have changed the face of how chemotherapy is given. Since the advent of these agents, chemotherapy patients are not as frequently transfused unless they are acutely ill with sepsis or a GI bleed.

Normal concentration of hemoglobin is considered to be 12 to 16 grams per deciliter (g/dL) for women and 14 to 18 g/dL for men. Anemia affects 13 to 80 percent of patients undergoing treatment for solid tumors. There is a wide variation in the percentage of patients who will develop anemia because of the various chemotherapy regimens used. Newer chemotherapy regimens may not necessarily include drastically myelosuppressive chemotherapy agents. Thirty to 40 percent of patients treated for lymphoma are going to be faced with anemia because most of the drugs that are used for treatment do have myelosuppressive capabilities.

Erythropoietin is a glycoprotein, which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation

of committed erythroid progenitors in the bone marrow.<sup>1</sup> Two erythropoiesis stimulating agents with the same biological effects as endogenous erythropoietin are available – epoetin alpha (Epogen<sup>®</sup>, Procrit<sup>®</sup>) and darbepoetin (Aranesp<sup>®</sup>).<sup>2-4</sup> Although these agents have many other indications, they are indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. They are indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of two months.

Erythropoietin (EPO) is a protein hormone that consists of 165 amino acids. It is made up of 60 percent protein and 40 percent carbohydrate with sialic acid residues. Epoetin alpha is identical to endogenous EPO. Darbepoetin has an increase in sialic acid residues, which increases the half life and duration of activity. Darbepoetin can be given at longer intervals because of its longer half-life.

Concerns with adverse effects of ESAs have risen in the last few years. One concern is that ESAs are not just growth factors for the erythrocytic series, but could be growth factors for tumor cells. Multiple cell types in the body express erythropoietin receptors. ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to target a hemoglobin of 12 g/dL.<sup>5</sup>

There have been at least six studies in patients with cancer that suggest a worse outcome when using ESAs. These studies were fraught with design problems, but they did show a higher mortality, a higher number of thrombotic events, and an increase in local recurrences in patients with some cancer. In five of the six studies, the target hemoglobin was greater than 12 g/dL. One study specifically aimed to have a target hemoglobin of 15 g/dL. Additionally, the patients studied were not receiving chemotherapy, which may have impacted the results. Whether these results apply to patients who actually meet the FDA indications remains to be proven.

A study published in 2007 found that using EPO in critically ill patients was not beneficial and may actually be harmful.<sup>6</sup> This study randomly assigned patients to receive weekly EPO 40,000 units versus placebo. They found that there was no difference in the number of packed red blood cell transfusions required and there was an increased number on the thrombotic events. There may have been some mortality benefit in the trauma subgroup of patients. This study illustrates there are situations where the use of EPO should be critically assessed, but this should be done appropriately without taking away from the benefits of these agents in the setting of cancer chemotherapy.

In 2007, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) published an updated clinical practice guideline on the use of epoetin and darbepoetin.<sup>7</sup> These two groups first published evidence-based guidelines for the use of epoetin in 2002. For the 2007 update, the ASCO-ASH Update Committee expanded the scope of the guideline to include recommendations to address the use of darbepoetin, compare the effectiveness of the available agents, and address thromboembolic risk associated with epoetin and darbepoetin.

The guidelines note that ESA therapy is a treatment option to increase hemoglobin and decrease transfusions for patients with chemotherapy-induced anemia. Based on a comprehensive systematic review of the literature comparing outcomes in chemotherapy-induced anemia, the guidelines consider the available agents to be equivalent with respect to effectiveness

and safety. The guidelines recommend assessment of patients for the causes of their anemia before receiving ESA therapy. The patient may have an anemia treatable with other means. The guidelines also recommend minimizing the use of ESA therapy in patients with high risk for thromboembolic events.

In the chemotherapy patient, the threshold for initiating therapy with ESA is a hemoglobin that is approaching or below 10 g/dL. Red blood cell transfusion also is an option if there are reasons to avoid using ESA therapy. For the patient who has a hemoglobin that is greater than ten but less than 12, options based on the clinical circumstances, are to use the ESA immediately or wait until the hemoglobin falls closer to 10 gm/dL. Again transfusion also is an option at this point.

The clinical circumstances that may dictate immediate use are an elderly individual with limited cardiopulmonary reserve, a patient with coronary artery disease or symptomatic angina, or the patient who has substantially reduced exercise capacity, energy, or ability to carry out activities of daily living. Many clinicians would be inclined to begin ESA therapy in a patient starting relatively intensive chemotherapy who is approaching ten.

Because of the increased risk of thromboembolism, the benefits of ESA therapy must be carefully weighed against the risks. In general, thromboembolic risk is increased in patients with a history of thromboses, undergoing surgery, who are immobilized, with limited activity, or with multiple myeloma who are being treated with either thalidomide or lenalidomide and doxorubicin or corticosteroids.

The FDA approved starting doses for epoetin at 150 units per kilogram three times a week or roughly 10,000 units, three times a week, subcutaneously or 40,000 units once a week subcutaneously. Weekly dosing is an advantage for patients. For darbepoetin, the starting dose is 2.25 micrograms per kilogram weekly or 500 micrograms every three weeks subcutaneously. There's no finding of consistent difference in outcomes from alternative starting doses or dosing schedules. Doses should be escalated based on response and according to the package labeling.

If there is insufficient response, therapy should be stopped after six to eight weeks. Insufficient response is defined as less than a 1 to 2 g/dL rise in hemoglobin or no decrease of transfusion requirements. This assumes appropriate dose increases were made according to the FDA approved labeling. Patients who have no response to ESA therapy should be evaluated for underlying tumor progression, iron deficiency, and other etiologies of anemia. Although this is how the guidelines define response and when to stop therapy for inadequate response, in some

Exhibit 1: 2007 Recommendations: Summary Justification for Initial Therapy

Justification for Initial Therapy	Consider other correctable causes of anemia first	Monitor and supplement iron	ESA <sup>1</sup>	Consider RBC Transition	Weigh the risk of thromboembolism
Chemotherapy-associated anemia and a Hb concentration approaching or below 10 g/dL	X	X	X	X	X
Chemotherapy-associated anemia with Hb concentration > 12 g/dL but never fallen near 10 g/dL	X	X	Use clinical circumstances to determine use	X	X
Patients with anemia associated with low-risk MDS	X	X	X	X	X
Anemia of cancer without chemotherapy with either solid or non-myeloid hematological malignancies	X	X	No	X	X
Myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia with concurrent chemotherapy	X	X	Only if Hb doesn't rise after chemotherapy and/or corticosteroids. Use caution, especially with people with multiple myeloma receiving thalidomide or lenalidomide and doxorubicin or corticosteroids.	X	X
High risk of thromboembolism	X	X	Minimize use.	X	X

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patients, clinicians will choose to continue therapy even though the hemoglobin has not increased. This is particularly true if the patient is receiving intensive chemotherapy and their hemoglobin is holding steady so no transfusions are required.

The ESA dose should be reduced if hemoglobin rises greater than 1 g/dL in any two week period or when the hemoglobin is greater than 11. Continuing at the same dose will cause the hemoglobin to reach or surpass 12 g/dL quickly. The risk of venous thromboembolism should be considered when determining dose reduction schedules. If someone is at very high risk for thromboembolic events, drastically reducing the dose or stopping at 11 should be seriously considered. The package labeling for the ESAs specifies how much the dose should be decreased.

Iron monitoring and supplementation may be valuable in limiting the need to increase the ESA dose. It may be valuable to maximize the symptomatic improvement as well as determining the reason for failure of these agents. Baseline iron studies should be obtained before the start of chemotherapy. Iron repletion should be instituted if needed. How frequently to repeat an iron study depends on the

hemoglobin response. There is inadequate evidence on the timing of repletion and frequency of iron store testing.

For patients with anemia who are not receiving chemotherapy, the evidence supports using ESAs in patients with anemia associated with low-risk myelodysplasia.<sup>7</sup> There are no published high-quality studies supporting exclusive ESA use in patients with anemic myeloma, non-Hodgkin's lymphoma, or chronic lymphocytic leukemia in the absence of chemotherapy.<sup>7</sup> The guidelines emphatically state that ESAs should not be used to treat anemia associated with malignancy among patients with either solid or non-myeloid hematological malignancies that are not receiving concurrent chemotherapy. This recommendation is consistent with the March 2007 black-box warning added to the labels of these agents.<sup>2-5</sup> Exhibit 1 provides a summary of justification for initial ESA therapy.

The guidelines suggest for patients with myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia that treatment begin with chemotherapy and/or corticosteroids to observe the hematologic outcomes from tumor reduction first. If an increase in hemoglobin is not seen following chemotherapy,

then ESA therapy is suggested. In many clinicians' experience, this approach results in a need for transfusion at the first cycle of chemotherapy. Non-Hodgkin's lymphoma is frequently treated with quite intensive and myelosuppressive chemotherapy regimens. In the treatment of patients with myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia, caution should be exercised in use of the ESAs concomitant with the chemotherapeutic agents and diseases where risks of thromboembolic complications is increased.<sup>7</sup> This is most important in myeloma treated with the newer agents that are not traditional chemotherapy, such as lenalidomide and thalidomide. Dexamethasone, erythromycin, and doxorubicin also have been associated with increased thromboembolic complications.

### Conclusion

ESA therapy is beneficial in decreasing the need for transfusions in patients who have cancer with chemotherapy-induced anemia. A number of published studies on ESAs for patients with cancer have raised safety concerns about tumor progression and thromboembolism. This led to new black box warnings being added to the labeling for ESAs. Updated

ASCO and ASH guidelines note that the available agents have similar efficacy and risks that must be considered. The data on the risks of these agents are incomplete. Healthcare professionals should consider the risks of tumor progression and decreased survival observed when ESAs are used as supportive care in patients with cancer. These risks should be carefully weighed against the need for and potential risks of blood transfusions. **JMCM**

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