Advantages of Every-3-Week Dosing of Erythropoietic Agents to Manage Chemotherapy-Induced Anemia

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Patients receiving chemotherapy for cancer often develop anemia, which can contribute to increased morbidity and reduced quality of life.[1] It is important for clinicians to be aware of current clinical studies in the treatment of chemotherapy-induced anemia. In patients with nonmyeloid malignancies, chemotherapy-induced anemia can be successfully treated using erythropoiesis-stimulating agents (ESAs). The application of these agents has evolved from more frequent to less frequent administration and from weight-based to single, fixed doses. Emerging data show that ESAs can be given safely on the same day as chemotherapy without loss of efficacy,[2] and that these agents may be administered as infrequently as every 3 weeks.[3,4] The every-3-week schedule is convenient and may reduce the burden on patients and their caregivers by reducing the number of visits to the clinic.

This commentary summarizes the latest studies of ESAs approved or under investigation in the United States for the treatment of chemotherapy-induced anemia (with a focus on every-3-week dosing). In addition, we offer clinicians a practical guide that incorporates and builds on current evidence-based anemia guidelines.[5,6]

Chemotherapy-Induced Anemia
Patients with cancer often suffer from chemotherapy-induced anemia, which is a debilitating condition resulting in increased transfusion requirements, increased fatigue, and reduced quality of life.[1] Historically, red blood cell (RBC) transfusions were the standard of care for the treatment of anemia and still may be utilized for patients with severe anemia (ie, hemoglobin levels < 8 g/dL, see Figure 1). Although transfusions can provide a quick correction of anemia, this correction is temporary and associated with potentially serious health risks such as transfusion reactions and infection, and over time with multiple transfusions, can predispose the patient to iron overload and secondary end-organ failure.[7] Transfusions are time-consuming and expensive, and deplete an important resource that is often in limited supply. Reducing requirements for RBC transfusions may lower these risks for patients with cancer-induced anemia.

Erythropoiesis-Stimulating Agents
ESAs can effectively treat anemia in patients undergoing chemotherapy by increasing hemoglobin concentrations and reducing or eliminating the requirements for RBC transfusions (see Key Points sidebar).[4,8-13] In addition, patients may have significantly improved quality of life and better physical and functional well-being after treatment with ESAs.[10,13-18] These agents act via the same mechanism as endogenous erythropoietin to stimulate RBC production in the bone marrow.[19]

The first recombinant human erythropoietin (rHuEPO) product was epoetin alfa, approved by the US Food and Drug Administration (FDA) as Epogen in 1989 and as Procrit in 1990. This agent dramatically changed the treatment of anemia and became one of the cornerstones of oncology supportive care. In 2002, a second-generation ESA, darbepoetin alfa (Aranesp), was approved for the treatment of cancer-induced anemia. Darbepoetin alfa stimulates RBC production to increase and
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Maintain hemoglobin levels by the same mechanism as epoetin alfa. However, darbepoetin alfa has a unique amino acid sequence and a greater sialic acid content, leading to a longer terminal half-life (approximately 74 hours in cancer patients), a longer duration of action, and greater biologic activity than rHuEPO (approximately 40 hours in cancer patients).[2,19,20] Another next-generation, long-acting ESA is the pegylated form of rHuEPO (Peg-EPO) that is said to have an erythropoietin receptor activator mechanism for stimulating erythropoiesis in a continuous manner. Peg-EPO is currently under phase II clinical trial investigation for its application in chemotherapy-induced anemia, using weekly and every-3-week administration.

Epoetin alfa was originally approved for three-times-weekly administration. Today, epoetin alfa is most often given as a weekly 40,000-unit dose. To date, one study has examined an extended dosing schedule of epoetin alfa in mildly anemic cancer patients using a front-loading approach (ie, 40,000 units weekly for 3 weeks followed by 120,000 units every 3 weeks vs 40,000 units weekly).[21] This showed no difference in overall transfusion rate between the treatment groups, but patients receiving the weekly dose were more likely to have greater than a 2 g/dL rise in hemoglobin; more likely to have their epoetin alfa dose held secondary to high hemoglobin; and had a higher final hemoglobin than the treatment group receiving 120,000 units every 3 weeks. Epoetin alfa currently does not have a label indication for extended dosing.

Darbepoetin alfa was initially approved for a weight-based weekly dosing of 2.25µg/kg. However, emerging data showed that darbepoetin alfa could be administered less frequently. Today, darbepoetin alfa is most commonly administered in clinical practice as a fixed 200-µg dose every 2 weeks.

The every-3-week schedule is becoming more common.[2-4,22-26] Last year, the weight-based 6.75 µg/kg every-3-week dosing regimen was approved for the treatment of chemotherapy-induced anemia in Europe. In the United States, every-3-week darbepoetin alfa (500 µg) for chemotherapy-induced anemia recently received FDA approval. The every-3-week dosing schedule has received attention because it coincides with the schedule for many common chemotherapy regimens. A retrospective review of nearly 3,000 patient records from 65 US oncology clinics revealed that 40% of chemotherapy was given on an every-3-week basis and 23% given on a weekly basis. Thus, 63% of these patients were receiving weekly or every-3-week chemotherapy regimens.[26] Consequently, the every-3-week dosing schedule may lead to increased convenience for health-care providers and their patients and have a favorable impact on clinical resource utilization.

Several studies have been published describing the optimal every-3-week dose. One double-blind, placebo-controlled, dose-response study showed that multiple weight-based doses of every-3-week darbepoetin alfa were effective (4.5, 6.75, 9, 12, 13, or 15 µg/kg).[4] with 4.5 µg/kg determined to be the minimally effective every-3-week dose (approximately 300 µg for a 74-kg patient). Limited incremental benefit was observed at doses above 6.75 µg/kg every 3 weeks. A recent study of 81 anemic patients provided further evidence of the effectiveness of darbepoetin alfa at 6.75 µg/kg (approximately 500 µg for a 74-kg patient) every 3 weeks regardless of the timing of administration relative to concurrent chemotherapy.[11] For ease in dosing, ESA therapy is increasingly being given to patients using fixed rather than weight-based doses.

Single, fixed doses of ESAs have been shown to be safe and effective.[12,14,18,24] The fixed-dose approach is commonly used in practice for weekly epoetin alfa at 40,000 units and for every-2-week darbepoetin alfa at 200 µg.[27] Recently, a clinical trial of darbepoetin alfa comparing the approved 2.25 µg/kg weekly dose to the every-3-week 500-µg dose showed comparable efficacy in achieving the targeted hemoglobin (77% vs 84%).[3,28] Furthermore, this study showed that roughly 75% of patients in both arms required a 40% dose reduction. The dose reduction was required to maintain hemoglobin levels in the desirable 11 to 13 g/dL range,[29,30] consistent with evidence-based practice guidelines.[5,6,31,32] Darbepoetin alfa is increasingly used every 3 weeks as a 300-µg dose in our practice (see the Case Study sidebar). The 500-µg and 300-µg doses correspond to the optimal and minimally effective every-3-week doses, respectively, for an average-weight patient of approximately 74 kg.[4]

Currently, there is some debate concerning the level of hemoglobin at which ESAs should be initiated. Subset analyses from several darbepoetin studies evaluated patient outcomes depending on whether ESAs were started when the hemoglobin was greater than or less than 10 g/dL.[33-35] In all of the studies, there was greater than a 50% reduction between the two groups in transfusions if ESAs were initiated at a hemoglobin > 10 g/dL. In addition, a study administering darbepoetin alfa 300 µg every 3 weeks showed that patients who started receiving darbepoetin alfa therapy in week 1 of chemotherapy maintained their hemoglobin levels within the National Comprehensive Cancer

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Network (NCCN) target range throughout the course of their treatment.[5] However, those who began darbepoetin alfa at 300 µg later in their treatment course after hemoglobin levels fell below 10 g/dL had a delay in achieving their target range generally after two doses (6 weeks).[33]

Iron Considerations

In patients with chemotherapy-induced anemia, a screening iron panel (serum iron, total iron binding capacity, serum ferritin) as well as B12 and folic acid levels should be obtained at baseline before starting ESA therapy. Supplements should be given if necessary. According to the NCCN guidelines, assessment of patients with no response to therapy should be performed after 4 weeks of epoetin alfa therapy and after 6 weeks of darbepoetin alfa therapy. It is important to recognize that in certain patients, a lack of response to ESA therapy is related to reduced iron levels. If no response is detected, a dose increase of the erythropoietic agent is recommended with or without iron supplementation.[5] The absorption of oral iron varies among patients within a fixed range, and intravenous iron supplementation is currently under investigation at many institutions.

Parenteral iron preparations include iron dextran (Dexferrum, InFeD), sodium ferric gluconate (Ferrlecit), and iron sucrose (Venofer), which are helpful in treating iron deficiency in patients intolerant of or unresponsive to oral iron therapy. These parenteral iron preparations are also useful for treating functional iron deficiency, both in cancer patients who are receiving ESAs and in chronic renal failure patients. Functional iron deficiency is particularly challenging, as the patient may appear to have adequate levels of iron, but the iron may not be biologically available for erythropoiesis. Thus, such patients may appear to have a lack of response to ESAs.

Benefits and Risks of ESAs

By increasing hemoglobin concentrations, ESAs can effectively treat anemia and the associated fatigue in patients undergoing chemotherapy.[4,8-13] Treatment of anemia with ESAs is associated with reduced transfusion requirements, improved quality of life, and better physical and functional well-being.[10,13-18] For many patients, control of fatigue means that they can maintain their normal work and leisure routines during chemotherapy. When ESA therapy is administered on an every-3-week schedule, patient convenience is increased and clinical resources are conserved. Therapy can often be administered in the same visit as chemotherapy.

Clinicians must also consider the risks of therapy for each patient, in order to determine the best treatment regimen and appropriate precautions. Blood pressure should be controlled in all patients before initiating therapy with erythropoietic agents, and should be monitored regularly during treatment. The risk of seizures is rare and has only been reported in chronic renal failure patients. ESAs may also increase the risk of thrombosis. In early trials, a high target hematocrit level (42% ± 3%) was associated with increased mortality and a higher number of arterial and venous vascular events. To minimize the risk of thromboembolic complications, the hemoglobin level should be targeted between 11 and 13 g/dL. Pure red blood cell aplasia has been reported in patients receiving ESAs. This condition is very rare and still not completely understood. Most of these cases occurred with Eprex, a form of epoetin alfa not sold in the United States.[5]

Is survival affected by the use of ESAs? Two studies have reported decreased survival in cancer patients receiving ESAs for the correction of anemia. However, these European studies of epoetin alfa and epoetin beta (NeoRecormon) by Leyland-Jones et al[36,37] and Henke et al,[38] respectively, were not conducted in anemic patients (ie, high hemoglobin levels were used for inclusion). Furthermore, the Henke et al study was conducted in the radiation oncology setting. A recent Cochrane meta-analysis of double-blind, randomized, placebo-controlled trials determined that the hazard ratio for overall survival associated with rHuEPO in 19 trials with 2,865 patients was 0.81 (95% CI = 0.67-0.99) for adjusted data and 0.84 (95% CI = 0.69-1.02) for unadjusted data, suggesting no negative impact on survival.[39] This analysis was recently updated to include four randomized placebo-controlled trials of darbepoetin alfa that were not included at the time of the original analysis. Pooled results suggest no negative impact on survival associated with ESA therapy for chemotherapy-induced anemia.[40]

In considering the risks of ESAs, it is important to remember that epoetin alfa, epoetin beta, and darbepoetin alfa are not identical to each other; each has its own risk-benefit profile and possibly its own effect on survival. Dosing, scheduling, and target hemoglobin values might also affect outcomes. In the trials that have shown decreased survival associated with ESA therapy, the majority of treated patients achieved higher hemoglobin levels than those currently recommended by evidence-based guidelines.[21]

Darbepoetin Alfa and Every-3-Week Dosing

Darbepoetin therapy can be initiated at the start of chemotherapy, and continued on an every-3-week schedule until chemotherapy is completed. The goal of ESA therapy should be to...
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Disclosures: Ms. Clark is a member of the speakers bureaus for OrthoBiotech and Amgen, and Dr. Schergen has conducted research for Amgen.

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