Extended-dosage-interval regimens of erythropoietic agents in chemotherapy-induced anemia

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Anemia is a frequent complication of cancer and chemotherapy and contributes to increased morbidity and mortality. The FDA-approved labeling for the erythropoiesis stimulating agents (ESAs) recombinant human erythropoietin (epoetin alfa) and darbepoetin alfa specifies use for the treatment of chemotherapy-induced anemia (CIA) in patients with nonmyeloid malignancies. Both agents have been shown to be effective in managing this condition by increasing hemoglobin (Hb) levels, reducing the need for red blood cell (RBC) transfusions, and improving patients’ quality of life (QOL). More recent studies, evaluating ESAs in CIA, have focused on the efficacy and safety of extended-dosage-interval regimens (e.g., every two or three weeks). Depending on the cancer treatment regimen, these extended-dosage-interval regimens may permit the coordination of care or the administration of chemotherapy drugs and ESAs during the same clinic visit. Timing the administration in this manner may enhance adherence to therapy and provide greater convenience for patient and caregiver, as well as improve resource use. In March 2006 FDA approved a labeling change for darbepoetin alfa that included the use of 500 μg every three weeks for the treatment of CIA.

Purpose. The safety and efficacy of extended-dosage-interval regimens of erythropoiesis-stimulating agents (ESAs) for managing chemotherapy-induced anemia (CIA) are reviewed.

Summary. Anemia is a frequent complication of chemotherapy. The ESAs epoetin alfa and darbepoetin alfa have been shown to safely and effectively manage CIA; comparable outcomes have been demonstrated between epoetin alfa 40,000 units once weekly and darbepoetin alfa 200 μg every two weeks. These commonly prescribed regimens necessitate extra clinic visits by cancer patients receiving cyclic chemotherapy. ESA administration can now often be synchronized with a three-week chemotherapy cycle because of the recent approval of darbepoetin alfa 500 μg every three weeks for CIA. However, in the Phase III trial providing the basis for this new dosage recommendation, more than 70% of patients required a 40% reduction in the dosage, resulting in an average dose of 375 μg every three weeks. The extended-dosage-interval regimens have not been associated with an increase in cardiovascular or thrombotic adverse events. Extended-dosage-interval regimens of epoetin alfa are under investigation and may provide additional alternatives. Synchronizing ESA therapy with scheduled chemotherapy visits would help minimize disruptions for patients and caregivers and improve the use of health care resources.

Conclusion. Administration of darbepoetin alfa every three weeks offers the convenience of synchronization of treatment with 21-day-cycle chemotherapy in many patients with CIA. Extended-dosage-interval regimens for epoetin alfa are being investigated and show promise.

Index terms: Anemia; Antineoplastic agents; Darbepoetin alfa; Dosage schedules; Epoetin alfa; Hematopoietic agents; Toxicity
In most studies of ESAs for the management of CIA, anemia is defined as an Hb concentration of <11 g/dL. Efficacy measures often include the percentage of patients achieving an Hb concentration of ≥11 g/dL and the percentage of patients maintaining Hb concentrations in the range of 11–13 g/dL. The effectiveness of ESA therapy may also be described by the hematopoietic response rate. Depending on the study, this may be defined as the proportion of patients achieving an increase in the Hb concentration of ≥1 or ≥2 g/dL from baseline or achieving a terminal concentration of ≥12 g/dL in the absence of RBC transfusions in the previous 28 days. Current guidelines recommend dosage adjustment of ESA therapy to maintain an optimal Hb concentration of 12 g/dL because of safety concerns associated with concentrations exceeding 13 g/dL. FDA recommends maintaining Hb concentrations in the 10–12 g/dL range. RBC transfusion requirements are usually reported from week 5 of ESA treatment until the end of the treatment period, since this is an endpoint accepted by regulatory agencies as sufficient for drug approval. Previous studies have demonstrated that RBC transfusion rates before five weeks of therapy have been completed may not accurately reflect the effectiveness of ESA treatment. Studies evaluating ESAs for CIA may report an early Hb response rate or the percentage of patients achieving an increase in the Hb concentration of ≥1 g/dL by treatment week 5; however, it has not been determined if this measure is a valid predictor of the overall response. In studies cited here, treatment periods were typically about 16 weeks.

Recently, Gosselin et al. suggested that traditional, single-time-point effectiveness measures (e.g., hematopoietic response, targeted Hb levels) may not reflect the efficacy of ESA therapy over the entire treatment period. Data from previously published clinical trials of ESAs for CIA suggest that the area under the concentration-versus-time curve for Hb may be a more clinically meaningful effectiveness measure, since the calculation uses weekly or monthly Hb levels determined throughout the study. However, the information supporting this effectiveness measure is limited. Prospective evaluations using this measure of effectiveness are warranted.

This article reviews the efficacy and safety of extended-dosage-interval regimens of epoetin alfa and darbepoetin alfa for managing CIA. CIA and its treatment are also discussed.

**Overview of CIA**

At least 50% of patients living with cancer develop anemia, which can be caused by a direct effect of the neoplasm, chemical factors produced by the cancer, or adverse effects of cancer treatment. Erythropoiesis can be suppressed in cancer because of a reduction in erythroid progenitor cells in the bone marrow and elevated levels of inflammatory cytokines. In addition, tissue hypoxia may blunt erythropoietin production by the kidneys. Estimates of cancer-associated anemia indicate that six tumor types account for more than 75% of cases: breast cancer, lung cancer, non-Hodgkin’s lymphoma (NHL), ovarian cancer, myeloma, and colorectal cancer.

Repeated cycles of chemotherapy have been shown to worsen anemia in cancer patients primarily as a result of myelosuppression but also because of RBC destruction and nephrotoxicity-related blunting of erythropoietin production. The frequency of CIA and its severity are determined by the extent of the disease, the chemotherapy regimen, radiation therapy, or a combination of these factors. For example, anemia has been associated with cisplatin-based therapies historically and with newer agents more recently, including taxanes, vinorelbine, and camptothecins. Anemia toxicity criteria developed by the National Cancer Institute and the World Health Organization can assist in determining the severity of anemia associated with various chemotherapy regimens.

### Table 1. Toxicity Grades for Chemotherapy-Induced Anemia

<table>
<thead>
<tr>
<th>Toxicity Scale</th>
<th>Hemoglobin Conc. for Indicated Toxicity Grade (g/dL)</th>
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<tbody>
<tr>
<td></td>
<td>0 (Normal)</td>
</tr>
<tr>
<td>NCI</td>
<td>WNL</td>
</tr>
<tr>
<td>WHO</td>
<td>&gt;11</td>
</tr>
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*Adapted from reference 19, with permission.

NCI = National Cancer Institute, WNL = within normal limits, WHO = World Health Organization.

WNL hemoglobin values are 12.0–16.0 g/dL for women and 14.0–18.0 g/dL for men.
similar symptoms) in the description of chemotherapy-related toxicities; the rate of low-grade fatigue was approximately 30%, with 10% of patients reporting severe fatigue. In a survey of 379 cancer patients with a history of chemotherapy, 91% of those who reported fatigue said it prevented a normal life, and 88% reported an alteration in daily routines. In 2000, an estimated 1.24 million cancer patients in the United States were receiving chemotherapy, and approximately 800,000 of these patients were anemic (Hb concentration, <12 g/dL), with only 26% (n = 210,000) being prescribed erythropoietic therapy. In 2000, an estimated 1.24 million cancer patients in the United States were receiving chemotherapy, and approximately 800,000 of these patients were anemic (Hb concentration, <12 g/dL), with only 26% (n = 210,000) being prescribed erythropoietic therapy.16

Anemia in cancer patients receiving chemotherapy is frequently undertreated because of cost issues and lack of knowledge about anemia’s incidence, sequelae, and management.16 In 2000, an estimated 1.24 million cancer patients in the United States were receiving chemotherapy, and approximately 800,000 of these patients were anemic (Hb concentration, <12 g/dL), with only 26% (n = 210,000) being prescribed erythropoietic therapy.16

Treatment options

Transfusions. RBC transfusions were the primary treatment for CIA until the early 1980s.19 Currently, this option is usually reserved for patients with severe or life-threatening anemia.4 With the approval of ESAs for the management of CIA, interventions can be more timely and safe, preserving QOL and reducing the potential need for RBC transfusions.4,5

ESA therapy. Recommendations for the initiation of ESA therapy in the management of CIA and for therapeutic goals have been published by the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the American Society of Hematology.5,6 The guidelines recommend starting ESA therapy at Hb concentrations of <10 g/dL; however, therapy may be considered at 10–11 g/dL. The goal of therapy is an Hb concentration of 12 g/dL.

Patients commonly develop a functional iron deficiency after continued ESA therapy.5 This condition reflects an inability to mobilize enough iron to meet the demands of erythropoiesis rather than an actual iron-storage deficiency. Generally, the deficiency is characterized by a transferrin-iron saturation percentage of <20%.2 Although oral iron is often prescribed, recent studies have suggested that i.v. iron therapy may be superior in terms of enhancing the response to ESA therapy and improving QOL.22,23 Three i.v. iron products are available: iron dextran, sodium ferric gluconate complex in sucrose, and iron sucrose. Adverse-event data suggest that sodium ferric gluconate complex in sucrose and iron sucrose are safer than iron dextran.24

Epoetin alfa. Epoetin alfa is a recombinant human erythropoietin product that has been available for over 10 years. Two epoetin alfa dosage regimens, 150 units/kg s.c. three times weekly and 40,000 units s.c. once weekly, are included in FDA-approved labeling for use in the management of CIA in patients with nonmyeloid malignancies.2 If the hematopoietic response to these initial dosages is not satisfactory, an increase to 300 units/kg three times weekly after eight weeks of therapy (with 150 units/kg three times weekly) or to 60,000 units once weekly after four weeks of therapy (with 40,000 units once weekly) is recommended.2

Darbepoetin alfa. Darbepoetin alfa is a glycoengineered protein analogue of epoetin alfa with a different primary structure accommodating an increased sialic acid residue content.3 This structural difference produces an extended serum elimination half-life (24–89 hours) that is more than 3 times longer than that of epoetin alfa (4–13 hours), allowing for less frequent administration. Darbepoetin alfa’s labeling was amended in 2001 to include the treatment of CIA in cancer patients with nonmyeloid malignancies at a starting dosage of 2.25 μg/kg s.c. once weekly. Increases to 4.5 μg/kg s.c. once weekly are recommended for patients with a rise in Hb concentration of less than 1 g/dL at week 6. In March 2006 FDA approved a labeling change that included the administration of 500 μg every three weeks for CIA.3

ESA use in clinical practice

Two large, retrospective medication-use evaluations have been conducted to examine patterns of ESA use for CIA in clinical practice, Hb responses, and associated RBC transfusion rates.25,26 The unlabeled regimen of 200 μg every two weeks for darbepoetin alfa and the labeled regimen of 40,000 units once weekly for epoetin alfa were the most commonly prescribed ESA regimens.27 The safety and efficacy of darbepoetin alfa every two weeks in patients with CIA were demonstrated in a randomized Phase II dose-finding study, with epoetin alfa 40,000 units once weekly as the active control.27 Two single-group clinical trials further assessed extended-dosage-interval darbepoetin alfa regimens by using a weight-based regimen with an initial dosage of 3 μg/kg every two weeks and a fixed-dose regimen of 200 μg every two weeks.28,29 Both trials indicated that darbepoetin alfa every two weeks was well tolerated and effective in a combined population of over 3600 patients with CIA.

Comparative studies of darbepoetin alfa versus epoetin alfa

Only a few head-to-head, prospective, randomized clinical trials have been conducted comparing commonly prescribed regimens of darbepoetin alfa and epoetin alfa for CIA. Each trial had a different design and a different primary endpoint.30-32 However, patient-enrollment criteria were similar and included anemic patients with a solid tumor who were scheduled to receive a specified number of chemotherapy cycles. The results of these studies, after accounting for protocol variations, suggest comparable efficacy and safety between darbepoetin alfa 200 μg every...
two weeks and epoetin alfa 40,000 units once weekly.

Schwartzberg et al. compared these regimens over 16 weeks in a randomized open-label trial in patients with breast, lung, or gynecologic cancer. A total of 318 anemic patients scheduled to receive at least eight additional weeks of chemotherapy were enrolled in the study. The primary endpoint was the validation of a patient-satisfaction questionnaire for anemia; however, secondary endpoints of hematologic efficacy and safety were also reported. The protocol permitted dosage escalation for both ESA regimens in patients with an increase in the Hb concentration of <1 g/dL after four weeks of treatment. In the final combined analysis of 312 patients, the mean change in Hb at the end of the ESA treatment period was 1.4 g/dL for darbepoetin alfa and 1.5 g/dL for epoetin alfa; the difference was not significant. Hematologic results, including hematopoietic response rates, the proportion of patients achieving the targeted Hb level, and the maintenance of this level for the remainder of the study, were also similar between groups. Kaplan–Meier estimates showed no significant difference in the median time to reach the targeted Hb level (five weeks for darbepoetin alfa and four weeks for epoetin alfa). Among patients with a baseline Hb concentration of <10 g/dL, the median time to the targeted Hb level was prolonged to seven weeks for darbepoetin alfa and eight weeks for epoetin alfa. Among patients with a baseline Hb concentration of ≥10 g/dL, targeted Hb levels were achieved in a more abbreviated time of three weeks in both treatment groups. There was no significant difference between groups in the percentage of patients requiring an RBC transfusion from month 1 to the end of ESA treatment (16% for darbepoetin alfa and 17% for epoetin alfa). The frequency of dosage adjustments was also similar between groups.

Waltzman et al. conducted a randomized superiority trial comparing these commonly prescribed regimens of darbepoetin alfa and epoetin alfa over 16 weeks in 352 patients with CIA who were undergoing ≥12 weeks of planned chemotherapy. The protocol-defined dosage escalation times for nonresponders (patients with an increase in the Hb concentration of <1 g/dL) differed between treatment groups and were specified at week 5 for epoetin alfa and at week 7 for darbepoetin alfa. Approximately 30% of patients in each group required a dosage increase at these times. The final analysis of the primary endpoint, an early increase in the Hb concentration of ≥1 g/dL by week 5, demonstrated a significantly higher response rate for epoetin alfa (47%) than for darbepoetin alfa (33%) (p = 0.0078). The Kaplan–Meier-adjusted estimates for the median time to this response were 35 days for epoetin alfa and 46 days for darbepoetin alfa (p = 0.0057). Mean increases in Hb levels from baseline were significantly higher in patients receiving epoetin alfa than in patients receiving darbepoetin alfa at all specified measurement times from week 3 to the end of the study (p ≤ 0.023). The percentage of patients requiring at least one RBC transfusion from week 5 to the end of ESA treatment—a period when each group was permitted a dosage adjustment—was similar between groups (13% for epoetin alfa and 18% for darbepoetin alfa) (p = 0.2936). The Hb response rates reported in this study were not consistent with those found in other evaluations of these dosage regimens. This may be partially due to differences between the therapies in protocol-specified dosage-escalation times.

In 2006, Glaspy et al. published the results of a large, randomized, prospective noninferiority trial comparing epoetin alfa 40,000 units once weekly with darbepoetin alfa 200 µg every two weeks that showed comparable efficacy and safety over 16 treatment weeks. A total of 1220 anemic patients undergoing eight or more weeks of planned chemotherapy were enrolled; 1209 patients were included in the final analysis. Dosage escalations were permitted for both treatment groups at week 5. Findings for the primary endpoint, the Kaplan–Meier-adjusted percentage of patients who received an RBC transfusion from week 5 to the end of treatment, were similar between groups (darbepoetin alfa, 21%; epoetin alfa, 16%). Since the upper limit of the 95% confidence interval of the difference between groups (10.8%) was below the prespecified noninferiority margin of 11.5%, noninferiority between the two therapies for RBC transfusion requirements during this period was established. The secondary transfusion endpoint (week 1 to the end of treatment) was consistent with the primary endpoint, confirming noninferiority. At weeks 9 and 17, the change in the Hb level from baseline was similar in both treatment groups. The targeted Hb concentration range (11–13 g/dL) was achieved by more than 75% of the patients in each group. The median time to reach this endpoint was 6 weeks (95% CI, 3–13 weeks) for darbepoetin alfa recipients and 5 weeks (95% CI, 3–9 weeks) for patients given epoetin alfa. A majority of the patients maintained Hb levels within the targeted range for the remainder of the treatment period.

Extended-dosage-interval strategies

A retrospective review of ESA utilization for CIA in 2785 patients found that 40% of the study population received chemotherapy on a 21-day cycle. This finding revealed an opportunity to reduce the number of oncology clinic visits and resource use by synchronizing ESA therapy with chemotherapy every three weeks. Recent studies have evaluated the safety and efficacy of various
extended-dosage-interval ESA regimens for CIA. Regimens investigated included three-week dosage intervals for darbepoetin alfa and two- and three-week dosage intervals for epoetin alfa.3,33-36

**Darbepoetin alfa.** Clinical studies have demonstrated that darbepoetin alfa administered at a fixed dosage of 300 or 500 µg every three weeks is safe and effective in the treatment of CIA. In a Phase II dose-finding study evaluating darbepoetin alfa every three weeks, 4.5 µg/kg was the minimally effective weight-based dose with respect to hematopoietic response and RBC transfusion requirements. Improvement was also seen with 6.75 µg/kg; larger doses did not provide an additional clinical benefit.37 The darbepoetin alfa fixed dosage of 300 µg every three weeks is derived from the weight-based dosage of 4.5 µg/kg every three weeks. The fixed dosage of 500 µg every three weeks is based on the 2.25-µg/kg once-weekly regimen for CIA that is included in the FDA-approved labeling for darbepoetin alfa.3,38

Taylor et al.33 found darbepoetin alfa 300 µg every three weeks to be well tolerated and safe in a 15-week, Phase III, randomized placebo-controlled trial. A total of 386 anemic patients who had a nonmyeloid malignancy and who were receiving ≥12 weeks of planned chemotherapy were included in the efficacy analysis.33 The percentage of patients in the darbepoetin alfa group (n = 161) and the placebo group (n = 166) who achieved the targeted Hb concentration (≥11 g/dL) was 77% (95% CI, 70–84%) and 55% (95% CI, 46–64%), respectively. The median time required to achieve the target Hb concentration was seven weeks (95% CI, six to eight weeks) in patients receiving darbepoetin alfa and 16 weeks (95% CI, 11 weeks to not estimable) in patients receiving placebo. Ninety-eight patients receiving darbepoetin alfa (67%) and 54 patients receiving placebo (52%) maintained an Hb level within the targeted range (11–13 g/dL) after initially achieving a target Hb concentration. The Kaplan–Meier-adjusted percentage of patients needing RBC transfusions from week 5 to the end of treatment was significantly lower in the darbepoetin alfa group (24% of 181 patients; 95% CI, 18–30%) than in the placebo group (41% of 185 patients; 95% CI, 34–49%) (p < 0.001). Darbepoetin alfa dosage escalations to 500 µg were permitted at week 4 in patients with an Hb concentration of <9 g/dL at week 7 in patients with an Hb concentration of <10 g/dL and an increase in Hb concentration of <1 g/dL. Dosages were reduced in patients with an Hb concentration of ≥13 g/dL or an increase of ≥1 g/dL over any two-week period. Twenty-four percent of patients required a dosage increase and 39% a dosage reduction. The mean dose administered every three weeks was 283.8 µg based on the reported mean ± S.D. once-weekly dose of 94.6 ± 24.5 µg.

A single-group open-label study by Boccia et al.34 also found darbepoetin alfa 300 µg every three weeks to be effective and safe for the management of CIA. Of the 1493 patients included in the efficacy-endpoint analysis, approximately one third had baseline Hb concentrations of <10 g/dL (mean ± S.D., 9.3 ± 0.6 g/dL); the remaining two thirds had values of ≥10 g/dL (mean ± S.D., 10.5 ± 0.3 g/dL). Otherwise, groups were well balanced according to baseline demographic and disease characteristics. As expected, a greater proportion of patients in the early-intervention group not only achieved the targeted Hb level but did so in a shorter time. However, once targeted levels were reached, there was little difference between groups in maintaining these levels throughout the remainder of the study. Fewer patients in the early-intervention group required a dosage escalation compared with the late-intervention group (37% versus 45%). In addition, the early-intervention group required fewer RBC transfusions during month 1.
of the study and from weeks 5 to 16. RBC transfusion requirements at month 4 were similar between groups. Sensitivity and specificity calculations were performed for both intervention groups to determine if an early rise in Hb concentration (≥21 g/dL during the first four treatment weeks) was a predictor of clinical outcomes in terms of RBC transfusion requirements and achievement of targeted Hb levels. Results indicated a low sensitivity.

Recently, FDA approved amending the labeling of darbepoetin alfa to include the dosage of 500 μg every three weeks in patients with CIA. The labeling change was based on the successful outcome of a Phase III double-blind noninferiority trial. A total of 705 anemic patients who had a nonmyeloid malignancy and were undergoing ≥12 weeks of planned chemotherapy were randomized to receive darbepoetin alfa 500 μg s.c. every three weeks or 2.25 μg/kg s.c. once weekly for up to 15 weeks. Baseline epidemiology and hematologic characteristics were similar between groups. Of 346 patients receiving darbepoetin alfa every three weeks, 84% (95% CI, 81–88%) achieved a targeted Hb level (≥11 g/dL), while 77% (95% CI, 72–81%) of 348 patients receiving the drug once weekly achieved a targeted level. The Kaplan–Meier-adjusted percentages of patients receiving an RBC transfusion from week 5 to the end of treatment for the extended-dosage-interval regimen versus the weekly-dose group were 23% (95% CI, 19–28%) of 335 patients and 30% (95% CI, 25–35%) of 337 patients, respectively. The darbepoetin alfa extended-dosage-interval regimen was noninferior to the once-weekly regimen, since the upper limit of the 95% CI for the difference in transfusion rates between groups was less than the protocol-specified margin of 12.5%. An additional analysis of RBC transfusion requirements from week 1 to the end of treatment yielded similar results. An assessment of transfusion requirements based on body-weight categories found no reduction in the efficacy of a darbepoetin alfa fixed-dose regimen with increasing body weight.

The two treatment groups had a similar change in Hb concentration from baseline to the end of treatment (a mean difference of −0.02% [95% CI, −0.27% to 0.23%]). A majority of patients in both groups who reached the targeted Hb level maintained a concentration in the targeted range (11–13 g/dL) for the remainder of the study. There was a small difference between the extended-dosage-interval and once-weekly groups in the time required to reach targeted levels (five and six weeks, respectively). A review of the FACT-F scores from baseline to the end of treatment showed that more than 50% of the patients in each treatment group had a significant improvement. The extended-dosage-interval regimen was not associated with an increased risk of cardiovascular or thromboembolic adverse events compared with the once-weekly regimen.

Approximately 75% of the patients in each group required a 40% dosage reduction, predominately because of Hb increases of ≥1 g/dL within a 14-day period (in the absence of RBC transfusions). Hb concentrations in-

### Table 2. Outcomes Associated with Baseline Hemoglobin Values of <10 and ≥10 g/dL in Patients Receiving Darbepoetin Alfa Every Three Weeks for Chemotherapy-Induced Anemia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline Hb &lt;10 g/dL (n = 462)</th>
<th>Baseline Hb ≥10 g/dL (n = 918)</th>
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<tbody>
<tr>
<td>No. (%) pts who achieved Hb conc. of ≥11 g/dL [95% CI]</td>
<td>305 (66 [61–70])</td>
<td>775 (87 [85–90])</td>
</tr>
<tr>
<td>No. (%) pts who maintained Hb conc. of 11–13 g/dL</td>
<td>215 (71)</td>
<td>589 (73)</td>
</tr>
<tr>
<td>KM-adjusted time to achieve Hb. conc. of ≥11 g/dL, wk (95% CI)</td>
<td>9 (8–10)</td>
<td>3 (NE–NE)</td>
</tr>
<tr>
<td>No. (%) pts who achieved hematopoietic response (95% CI)</td>
<td>268 (58 [54–63])</td>
<td>606 (66 [63–69])</td>
</tr>
<tr>
<td>No. (%) pts who received RBC transfusion from wk 5 to end of study [95% CI]</td>
<td>121 (28 [24–32])</td>
<td>106 (12 [9–14])</td>
</tr>
<tr>
<td>% pts who received RBC transfusion in mo 1 vs. mo 4</td>
<td>22 vs. 3</td>
<td>5 vs. 3</td>
</tr>
<tr>
<td>% pts who had ≥3-point change in FACT-F score at wk 16 (95% CI)</td>
<td>58 (53–64)</td>
<td>53 (49–57)</td>
</tr>
<tr>
<td>Mean every-three-week dose administered, μg (95% CI)</td>
<td>331.1 (325.8–336.3)</td>
<td>319 (315.5–322.6)</td>
</tr>
<tr>
<td>No. (%) pts who had dosage increase</td>
<td>207 (45)</td>
<td>336 (37)</td>
</tr>
</tbody>
</table>

1Hb = hemoglobin, CI = confidence interval, KM = Kaplan–Meier, NE = not estimable, RBC = red blood cell, FACT-F = Functional Assessment of Cancer Therapy—Fatigue subscale.

2Increase in Hb conc. from baseline of 2 g/dL or Hb conc. of ≥12 g/dL in the absence of an RBC transfusion within the preceding 28 days.

3n = 431.

4n = 881.

5n = 343 at month 4.

6n = 749 at month 4.

7n = 303.

8n = 647.
increased at a rate of 0.34 g/dL/wk until the first dosage reduction, at which time they stabilized. The median time to the first dosage reduction was similar between the extended-dosage-interval and once-weekly groups (36 and 43 days, respectively). Accounting for dosage adjustments, the estimated darbepoetin alfa dose in the group receiving the drug every three weeks was 375 µg based on the reported average weekly dose of 125 µg, and the average dose for the once-weekly group was 107.8 µg.8

**Epoetin alfa.** In clinical practice, epoetin alfa is usually given weekly for the management of CIA.25,26 However, in recent years a modest number of studies have investigated extending the dosage interval to enhance convenience. Some of these studies have evaluated front loading, or the administration of more frequent doses for a scheduled number of weeks or until a specific Hb level is reached.35,40-42 This induction phase is followed by a maintenance phase in which the same or a higher dose is administered less frequently.

Steenisma et al.35 conducted a Phase III open-label comparative study in 365 patients with CIA who were started on epoetin alfa 40,000 units once weekly for three weeks (front-loading phase). The patients were then randomized either to continue this regimen (once-weekly group, n = 183) or to receive 120,000 units every three weeks (extended-dosage-interval group, n = 182) for an additional 18 weeks (maintenance phase). Dosage reductions but not increases were permitted for patient inclusion in the study. Eligible patients were anemic because of either a nonmyeloid cancer or chemotherapy, and concurrent chemotherapy treatments were not required (however, 89% of the enrolled patients were actively receiving chemotherapy). The primary efficacy endpoint, the percentage of patients who received an RBC transfusion, was comparable between groups for the entire study period (23% in the once-weekly group and 18% in the extended-dosage-interval group) (p = 0.22), as well as for the maintenance phase (13% and 15%, respectively) (p = 0.58). However, the once-weekly group had a greater Hb response than the extended-dosage-interval group, including a higher mean ± S.D. end-of-study Hb concentration (12.0 ± 1.5 versus 11.5 ± 1.5 g/dL, respectively; 95% CI for the difference in means, 0.2–0.8 g/dL) (p = 0.0006) and a greater mean ± S.D. increase in Hb concentration from baseline to the last measured value (1.8 ± 1.6 versus 1.4 ± 1.6 g/dL, respectively; 95% CI for the difference in means, 0.1–0.8 g/dL) (p = 0.01). Patients in the once-weekly group were more likely to have a drug dose withheld because of Hb concentrations exceeding 13 g/dL. Adverse events, overall survival, and QOL measures were similar between groups. Potential limitations of this study included a lack of blinding and a greater frequency of Hb assessments in the once-weekly group. In addition, the enrollment of patients with a higher mean Hb concentration (10.1 g/dL) may have produced a relatively low transfusion rate compared with other studies. Further studies are needed to investigate the clinical benefits of this extended-dosage-interval regimen.

A randomized, open-label, 13-week study by Henry et al.36 compared epoetin alfa 80,000 units every two weeks with 40,000 units once weekly in anemic patients who had nonmyeloid malignancies and were undergoing planned chemotherapy for ≥12 weeks. Regimens were modified to maintain Hb concentrations at approximately 12 g/dL. The primary efficacy endpoint, the mean change in Hb from baseline to the end of the study, was analyzed for the per-protocol population of 148 patients (72 patients receiving epoetin alfa every two weeks and 76 in the once-weekly group). Results for this endpoint were comparable between groups: 1.6 and 1.8 g/dL in patients receiving epoetin alfa every two weeks and those receiving the drug once-weekly, respectively. The Kaplan–Meier-adjusted percentages of patients receiving RBC transfusions from day 29 to the end of the study were also similar: 9.6% and 11.1%, respectively, for the per-protocol population (p = 0.709). More patients in the once-weekly group had doses withheld because of high Hb levels (>13 g/dL) or had dosage reductions because of a rapid rise in Hb concentration (>1 g/dL in any two-week period). Thirteen percent of the patients who received epoetin alfa every two weeks were switched to once-weekly administration, and 37% of the patients in the once-weekly group required a dosage increase because the Hb response was inadequate. The rates of clinically relevant thrombovenous events were similar between groups (7.8% for the patients who received epoetin alfa every two weeks and 7.6% for those who received epoetin alfa once weekly), as were the death rates (6.5% and 6.2%, respectively).

Other extended-dosage-interval regimens of epoetin alfa have been evaluated.40-42 Although these studies suggest positive outcomes in terms of hematologic response and RBC transfusion requirements, more research is warranted before conclusions about the most safe and effective regimen can be made.

**Convenience and efficiency of ESA administered every three weeks**

Cancer patients undergoing every-three-week chemotherapy need to schedule additional clinic visits to receive ESA treatment once weekly or every two weeks. Fortner et al.43 found that 83% of patients required assistance with transportation to and from a clinic. Patients and caregivers must often take time off from work to accommodate appointment times. Synchronizing the administration of ESA therapy with scheduled chemo-
Therapy visits would help minimize disruptions for patients and caregivers and improve the use of health care resources.

Chemotherapy for breast and other gynecologic cancers is often scheduled on a 21-day cycle.25 Women diagnosed with breast cancer, particularly those who are younger, may be the primary or only providers for their families and often work outside the home.44 These patients, too, would benefit greatly from cycle-to-cycle administration of an ESA. The effectiveness of darbepoetin alfa every three weeks in breast cancer patients has been demonstrated. Silberstein et al.45 reviewed data for a subset (n = 354) of patients with breast cancer who were enrolled in the trial by Boccia et al.34 and reported comparable results, with 83% of patients achieving the targeted Hb concentration (≥11 g/dL) and 77% maintaining Hb within the targeted range (11–13 g/dL). In addition, increases in Hb were correlated with clinically significant improvements in QOL.

Glaspy et al.46 evaluated the efficacy of darbepoetin alfa 6.75 µg/kg every three weeks in anemic patients with breast cancer (n = 32) versus efficacy in all anemic cancer patients enrolled in the study (n = 81). The mean change in Hb concentration from baseline to week 6 of therapy was similar between the breast cancer patients (1.2 g/dL; 95% CI, 0.8–1.5 g/dL) and all patients (1.0 g/dL; 95% CI, 0.7–1.3 g/dL). Hematopoietic response rates (an increase in the Hb concentration of ≥2 g/dL from baseline or a concentration of ≥12 g/dL) were also similar between groups (78% and 74%). These results were consistent whether the ESA was administered on a synchronous schedule (chemotherapy day 1) or an asynchronous schedule (chemotherapy day 15).

Gorem47 found darbepoetin alfa every three weeks to be effective in a small prospective pilot study enrolling 14 anemic women receiving chemotherapy for gynecologic malignancies, including breast cancer. A simplified front-loaded darbepoetin dosage regimen (6.75 µg/kg followed by 4.5 µg/kg every three weeks) was administered for up to six doses. (This regimen was previously evaluated by Glaspy et al.46) Five patients (36%) achieved a complete hematopoietic response (an increase in the Hb concentration ≥2 g/dL without an RBC transfusion), and four patients (28%) achieved a partial response (an Hb concentration increase of <2 g/dL without an RBC transfusion), resulting in an overall 64% response rate. The mean change in the Hb concentration was 1.6 g/dL (95% CI, 0.8–2.41 g/dL), and the mean maintenance dose administered every three weeks for this group was 303.2 µg (95% CI, 299.1–311.2 µg). QOL was improved among the six patients completing a posttreatment survey.

ESAs administered every three weeks may enhance economic outcomes for oncology clinics. A patient receiving a weekly ESA dose may be expected to return to the clinic two additional times for drug administration during a standard three-week chemotherapy cycle. With the advent of longer-acting growth factors, visits for ESA administration can be reduced and clinic resources redirected. Generally, the reimbursement for a growth factor injection is 1/20 the reimbursement for a chemotherapy treatment.49 Therefore, it is financially desirable for health care systems to provide more chemotherapy and fewer ESA injections. Two studies have found that the frequency of ESA administration declined significantly when longer-acting agents were used.50,51

Summary

Anemia is a frequent complication of chemotherapy and can negatively impact clinical and QOL outcomes. Epoetin alfa and darbepoetin alfa have been shown to safely and effectively manage CIA. Head-to-head studies have demonstrated comparable outcomes between epoetin alfa 40,000 units once weekly and darbepoetin alfa 200 µg every two weeks. For the many cancer patients receiving cyclic chemotherapy, these commonly prescribed ESA regimens necessitate extra clinic visits and consume additional health care resources.

ESA administration can now often be synchronized with a 21-day chemotherapy cycle because of the recent approval of darbepoetin alfa 500 µg every three weeks for the management of CIA. However, in the Phase III trial providing the basis for this new dosage recommendation, more than 70% of patients required a 40% reduction in the dosage, resulting in an average dose of 375 µg every three weeks. This dosage is more consistent with the findings of previous studies concluding that darbepoetin alfa, at an initial fixed dose of 300 µg every three weeks, is effective in the management of CIA. The extended-dosage-interval regimen has not been associated with an increase in cardiovascular or thrombotic adverse events. Extended-dosage-interval regimens of epoetin alfa are currently under investigation and may provide additional alternatives.

Conclusion

Administration of darbepoetin alfa every three weeks offers the convenience of synchronization of treatment with 21-day-cycle chemotherapy in many patients with CIA. Extended-dosage-interval regimens for epoetin alfa are being investigated and show promise.

FDA issued safety alerts on November 16, 2006, February 16, 2007, and March 9, 2007, regarding the use of ESAs.52 The alerts advised that analyses of four studies in patients with cancer revealed higher rates of serious and life-threatening adverse effects or death with the use of ESAs; these studies investigated an
unlabeled dosage regimen, a patient population for which ESAs are not approved, or an investigational ESA. Another study observed a higher rate of deep vein thrombosis in patients who received epoetin alfa at the approved dosage. The risks noted in these studies were consistent with those observed in previous studies of patients with chronic renal failure who received an unlabeled regimen of an ESA. FDA issued a black box warning that strongly recommended using the lowest effective ESA dosage, maintaining a target Hb concentration range of 10–12 g/dL, and closely monitoring for adverse cardiovascular events.

In May 2007, FDA’s Oncologic Drugs Advisory Committee (ODAC) reviewed previous and newly available data on the use of ESAs in cancer patients. Serious and life-threatening events were noted, including an increase in thromboembolic events, an increase in tumor progression, and a decrease in overall survival. ODAC made a number of recommendations to FDA, including initiating further research to clearly define the benefits and risks of ESA therapy, identifying Hb levels necessary for therapy initiation in asymptomatic patients, limiting ESA use according to specific tumor types, and discontinuing ESA therapy and monitoring patients after the completion of chemotherapy.

The Centers for Medicare and Medicaid Services issued a national coverage decision on July 30, 2007, with an immediate effective date, that restricts the use of these agents to patients with Hb concentrations of <10 g/dL, limits duration of ESA treatment after chemotherapy ends, and allows a one-time dose escalation of 25% at 4 weeks. Other restrictions are being enforced, but FDA-approved doses will be reimbursable to Medicare recipients.

References
THERAPY UPDATE  Erythropoietic agents


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