

Cancer Support Innovations

Extended Erythropoietic Stimulating Protein Dosing in Chemotherapy-Induced Anemia

Anemia is a frequent complication of cancer or chemotherapy and contributes to increased morbidity and mortality.¹ The erythropoietic stimulating proteins (ESPs), epoetin alfa and darbepoetin alfa, are approved by the Food and Drug Administration (FDA) for the treatment of chemotherapy-induced anemia (CIA) in patients with nonmyeloid malignancies^{2,3} (**Table 1**). These agents are effective in the management of CIA by increasing hemoglobin (Hb) levels, reducing the need for red blood cell (RBC) transfusions, and improving patients' quality of life (QOL).⁴ Recent studies, evaluating ESPs in CIA, have focused on the efficacy and safety of extended dosage regimens [e.g. every two week (Q2W) or every three week (Q3W) administration]. These regimens may permit the coordination of care or the administration of both chemotherapy and the ESP during the same clinic visit. Timing the administration in this manner may enhance compliance to therapy and provide greater convenience for the patient and caregiver, as well as improve resource utilization for the clinic. In March of 2006, the FDA approved the Q3W administration of darbepoetin alfa, 500 mcg, for the treatment of CIA.³ This newsletter focuses on novel, extended-dosing strategies for epoetin alfa and darbepoetin alfa.

Chemotherapy-Induced Anemia (CIA)

Repeated cycles of chemotherapy may escalate anemia in cancer patients primarily due to myelosuppression but also due to the destruction of RBCs and blunting of erythropoietin production as a result of nephrotoxicity.^{5,6} The rate and severity of CIA depends on numerous factors including the type, schedule and intensity

of the chemotherapeutic regimen and a previous history of myelosuppressive and/or radiation therapy.⁷ Anemia toxicity criteria, developed by organizations such as the National Cancer Institute (NCI) and the World Health Organization (WHO), can assist in determining the severity of anemia associated with various chemotherapeutic regimens⁷ (**Table 2**). Results of a retrospective review, focusing on regimens commonly used in breast and ovarian cancer, non-Hodgkin's lymphoma (NHL) and non-small cell lung cancer (NSCLC), reported a 10 to 68% incidence of mild to moderate anemia and a 5 to 79% incidence of severe to life-threatening anemia.^{7,8}

Chemotherapy-induced anemia in cancer patients is frequently undertreated due to many factors including a knowledge gap pertaining to the incidence and associated sequelae, uncertainties in management, and the cost of treatment and reimbursement issues.⁹ An estimated 1.3 of the 10 million cancer patients in the U.S. are anemic (Hb < 12 g/dL). Approximately 800,000 of these patients are receiving chemotherapy with only 26% (n = 208,000) prescribed erythropoietic therapy.⁹

Treatment Options

Recommendations for the initiation of ESP therapy in CIA along with therapeutic goals have been published by two groups, the American Society of Clinical Oncologists/American Society of Hematologists (ASCO/ASH) and the National Comprehensive Cancer Network (NCCN).⁸ The initiation of ESP therapy is recommended at Hb levels < 10 g/dL (ASCO/ASH) and ≤ 11 g/dL (NCCN). Goals for ESP therapy are target Hb levels of 12 g/dL.

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Epoetin alfa

Epoetin alfa (Procrit®, Ortho Biotech Products, LP; Raritan, NJ) is recombinant human erythropoietin and has been available in the U.S. for over 10 years. Two epoetin alfa regimens, 150 units/kg subcutaneously three times weekly (TIW) and 40,000 units subcutaneously once weekly (QW), are FDA-approved for the management of CIA in patients with nonmyeloid malignancies.² If the hematopoietic response to these initial doses is not satisfactory, increases to 300 units/kg TIW after 8 weeks of therapy or 60,000 units QW after 4 weeks of

therapy, respectively, are recommended² (Table 1).

Darbepoetin alfa

Darbepoetin alfa (Aranesp®, Amgen Inc.; Thousand Oaks, CA) 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 approximately three-fold longer than epoetin alfa (4 – 13 hours), allowing for less frequent administration. Darbepoetin alfa labeling was amended by the FDA in 2001 to

include the treatment of CIA in cancer patients with nonmyeloid malignancies at a starting dose of 2.25 mcg/kg subcutaneously QW. Increases to 4.5 mcg/kg subcutaneously QW at week 6 are recommended for a less than 1 g/dL rise in Hb. In March, 2006, the FDA approved the Q3W administration of darbepoetin alfa at a dose of 500 mcg for the treatment of CIA³ (Table 1).

Real-World Practice

Two large retrospective medication use evaluations (MUEs) in CIA were conducted examining usage patterns, Hb response, and transfusion rates

associated with ESP treatment in real-world clinical practices.^{10,11} MUE results revealed the most common dose and schedule for darbepoetin alfa in CIA was 200 mcg Q2W, and 40,000 units QW for epoetin alfa. Only a few head-to-head, prospective, randomized clinical trials (RCTs) have been conducted comparing these commonly prescribed regimens in CIA.¹²⁻¹⁴ Results of these studies, accounting for protocol variations, suggest comparable efficacy and safety between the two regimens.

Extended Administration Strategies

A retrospective review of CIA, conducted by Herrington *et al* in 2,785 patients, revealed that 40% of the study population received chemotherapy on a 21-day cycle.¹⁰ This finding demonstrates a potential opportunity to reduce oncology clinic visits and resource utilization by coordinating Q3W ESP therapy with cyclic chemotherapy. Recent studies have evaluated the safety and efficacy of various extended ESP regimens in CIA. Every-three-week regimens have been investigated for darbepoetin alfa, as well as Q2W and Q3W regimens for epoetin alfa.¹⁵⁻¹⁹

Darbepoetin alfa

The results of clinical studies have demonstrated that darbepoetin alfa, administered at a dose of 300 mcg or 500 mcg, Q3W, is safe and effective in the treatment of CIA¹⁵⁻¹⁷ (Table 3). Taylor *et al* found darbepoetin alfa 300 mcg Q3W to be well tolerated and safe in a 15-week, phase 3, randomized, placebo-controlled trial. A total of 386 anemic patients, with a nonmyeloid malignancy and ≥ 12 weeks of planned chemotherapy, were included in the efficacy analysis¹⁵ (Table 3). For the KM percentage of RBC transfusions from week 5 to the end of the treatment phase (EOTP), the darbepoetin alfa group demonstrated an almost 2-fold lower requirement compared to placebo (24% vs. 41%, respectively, P < 0.001). In addition, the proportion of patients achieving the target Hb range (11-13 g/dL) was significantly higher in the darbepoetin alfa group with a median time of 7 weeks. Twenty-four percent of patients required a dosage increase for an unsatisfactory Hb response with 39% undergoing a dose reduction due to an excessive rise in Hb. The mean Q3W dose was 283.8 mcg based on the reported mean QW dose, 94.6 mcg.

A single arm, open label study conducted by Boccia *et al*, entitled

“Synchronicity,” also found darbepoetin alfa 300 mcg Q3W to be an effective and safe regimen in the management of CIA¹⁶ (Table 3). Of the 1,493 patients included in efficacy endpoint analysis, 79% achieved a target Hb level (≥ 11 g/dL) at a median time of 4 weeks, with 73% maintaining Hb levels in the target range (11-13 g/dL) at 16 weeks. Results of secondary outcomes were also favorable, with 63% of patients achieving a hematopoietic response (2g/dL Hb increase or Hb ≥ 12 g/dL in the absence of a RBC transfusion within the previous 28 days) and 18% requiring a RBC transfusion from week 5 until the end of the study. A clinically significant improvement in Functional Assessment of Cancer Therapy-Fatigue (FACT-F) score was seen in 55% of patients. Thirty-nine percent of patients underwent a dose escalation to 500 mcg at week 7 due an unsatisfactory Hb response and 21% had a dose reduction due to a > 1 g/dL Hb level increase in a 2-week period. The mean Q3W dose administered was 323.6 mcg.

Previous data has suggested that ESP therapy initiated at Hb levels ≥ 10 g/dL (early intervention) is associated with improved and expedited outcomes compared to the initiation of

Table 1: Erythropoietic stimulating proteins commercially available for use in chemotherapy-induced anemia

Generic Name	Brand Name	FDA-Approved Indications ^a	Availability	FDA-Approved Dose for CIA	Alternate Dosing in CIA
Epoetin alfa	Procrit ²	-Treatment of anemia of CRF -Treatment of anemia in zidovudine-treated HIV-infected patients -Treatment of anemia in cancer patients with non-myeloid malignancies on chemotherapy -Reduction of allogenic blood transfusions in surgery patients	Single-dose vials 2,000, 3,000, 4,000, 10,000, 40,000 units Multidose vials 10,000, 20,000 units	150 units/kg subcut TIW with escalation to 300 units/kg subcut TIW for unsatisfactory response ^b <i>or</i> 40,000 units subcut QW with escalation to 60,000 units subcut QW for unsatisfactory response ^c	80,000 units subcut Q2W ¹⁹
darbepoetin alfa	Aranesp ³	-Treatment of anemia of CRF -Treatment of anemia in cancer patients with non-myeloid malignancies on chemotherapy	Single dose vials/ pre-filled syringes 25, 40, 60, 100, 200, 300, 500 mcg	2.25 mcg/kg subcut QW with escalation to 4.5 mcg/kg subcut QW for unsatisfactory response ^d 500 mcg subcut Q3W	200 mcg subcut Q2W ¹⁴ 300 mcg subcut Q3W ^{15,16}

^a FDA = Food and Drug Administration, CIA = chemotherapy-induced anemia, CRF = chronic renal failure, HIV = human immunodeficiency virus, subcut = subcutaneous, TIW = three times a week, QW = every week, Q2W = every two weeks, Q3W = every three weeks

^b No reduction in transfusion requirements or rise in hemoglobin after 8 weeks

^c < 1 g/dL increase in hemoglobin after 4 weeks in the absence of a RBC transfusion

^d < 1 g/dL increase in hemoglobin after 6 weeks in the absence of a RBC transfusion

Table 2: Anemia Toxicity Scales^{7,8}

Grade	0 (normal)	1 (mild)	2 (moderate)	3 (severe)	4 (life-threatening)
NCI Scale ^a Hb (g/dL)	14 – 18 (men) 12 – 16 (women)	≥ 10	8 – 10	6.5 – 7.9	< 6.5
WHO Scale Hb (g/dL)	> 11	9.5 – 10	8 – 9.4	6.5 – 7.9	< 6.5

^a NCI = National Cancer Institute, Hb = hemoglobin, WHO = World Health Organization

Source: Adapted from Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst.* 1999;91:1616-34.

therapy at Hb levels < 10 g/dL (late intervention).²⁰ *Boccia et al* stratified the Synchronicity study population according to the baseline Hb level at ESP therapy initiation and reported similar results¹⁶ (Table 4). Of the 1,493 patients included in the efficacy endpoint analysis, approximately one-third had baseline Hb levels < 10 g/dL, with the remaining two-thirds at a baseline Hb levels ≥ 10 g/dL. A greater proportion of patients in the early intervention group not only achieved the target Hb level but did

so in a shorter timeframe. However, once target 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 dose escalation compared to the late intervention group (37% versus 45%, respectively). In addition, patients in the early intervention group required fewer RBC transfusions during month 1 of the study and from week 5 to 16.

Most recently, the FDA approved the Q3W dosing of darbepoetin alfa, 500 mcg, for CIA based on a phase 3, doubleblind, noninferiority trial conducted by *Canon et al*¹⁷ (Table 3). A total of 705 anemic patients, with a nonmyeloid malignancy and ≥ 12 weeks of planned chemotherapy, were randomized to receive darbepoetin alfa 500 mcg Q3W or 2.25 mcg/kg QW for up to 15 weeks (EOTP). The darbepoetin alfa Q3W regimen was determined to be noninferior to the QW regimen according to KM

estimates of the percentage of patients who received a RBC transfusion from week 5 to the EOTP, 23% versus 30%, respectively. An additional analysis of RBC transfusion requirements from week 1 to the EOTP yielded similar results confirming noninferiority.

In reviewing additional outcomes, the two treatment groups had a similar change in Hb concentration from baseline to the EOTP [a mean difference (95% CI) of -0.02 percentage points (-0.27, 0.23)]. A trend for a higher proportion of

patients in the Q3W week to achieve the target Hb level (≥ 11 g/dL) was demonstrated. The majority of patients in both groups, who reached the target Hb level, maintained Hb levels in the target range (11-13 g/dL) for the remainder of the study. There was only a small difference between groups in the time required to reach target levels (5 weeks versus 6 weeks, Q3W versus QW, respectively). In review of the FACT-F scores from baseline to the EOTP, more than 50% of the patients in each treatment group had a signif-

icant improvement. In terms of safety, the Q3W regimen was not associated with an increased incidence of cardiovascular or thromboembolic adverse events when compared with the QW dosing schedule.¹⁷

Approximately 75% of the patients in each group required a 40% dose reduction at least once during the study due to Hb level increases of ≥ 1 g/dL within a 14 day period (in the absence of RBC transfusions). The median time to the first dose reduction was similar between the Q3W and

Table 3: Clinical Data for Darbepoetin alfa Administered Every-Three-Weeks in Chemotherapy- Induced Anemia

Outcomes	Placebo-controlled trial ^{15,a}		Single-arm, open-label trial ¹⁶	Head-to-head comparison ¹⁷	
	Placebo	300 mcg subcut Q3W		2.25 mcg/kg subcut QW	500 mcg subcut Q3W
Darbepoetin alfa regimen	Placebo	300 mcg subcut Q3W	300 mcg subcut Q3W	2.25 mcg/kg subcut QW	500 mcg subcut Q3W
Number of patients	193	193	1,493	352	353
Patients who achieved a target Hb level ^b % (95% CI) [n]	55% (46,64) ^c [166]	77% (70,84) ^c [161]	79% (77,81) ^d [1464]	77% (72,81) ^c [346]	84% (81, 88) ^c [348]
Median time to achieve target Hb (95% CI)	16 weeks (11, NE)	7 weeks (6,8)	4 weeks ^c (4,5)	6 weeks ^c	5 weeks ^c
Number of patients who maintained Hb level in target range ^e after achieving target level (%)	54 (52%)	98 (67%)	858 (73%)	NR	NR
Patients who received a RBC transfusion from week 5 – EOS % (95% CI) [N]	41% (34,49) ^c [185]	24% (18-30) ^c [181]	18% (16-20) ^d [1417]	30% (25-35) ^c [337]	23% (19-28) ^c [335]
Mean Q3W dose administered (95% CI)	NA	283.8 mcg ^f	323.6 mcg (320.8– 326.4)	NA	375 mcg ^f

^a Q3W = every three weeks, subcut = subcutaneous, Hb = hemoglobin, CI = confidence interval, NE = not estimable, NR = not reported, NA = not applicable, KM = Kaplan-Meier estimation, RBC = red blood cell, EOS= end of study

^b ≥ 11 g/dL

^c Kaplan-Meier estimate

^d crude percent indicates actual number of patients

^e 11-13 g/dL

^f Based on reported mean QW dose for the Q3W regimen study group

Table 4: Early Versus Late Intervention with Darbepoetin alfa Administered Every-Three-Weeks in Chemotherapy-Induced Anemia¹⁶

Outcomes ^a	Late intervention Baseline Hb < 10g/dL	Early intervention- Baseline Hb > 10 g/dL
Number of patients	462	918
Patients who achieved a target Hb level ^b % (95% CI) [N]	66% (61-70) [462]	87% (85-90) [891]
Number of patients who maintained a Hb in the target range ^c after achieving a target level (%)	215 (71%)	539 (73%)
KM time to achieve target Hb (95% CI)	9 weeks (8-10)	3 weeks (NE- NE)
Patients who achieved a hematopoietic response ^d Crude percent ^e (95% CI) [N]	58% (54-63) [462]	66% (63-69) [918]
Patients who received a RBC transfusion from week 5 - EOS Crude percent (95% CI) [N]	28% (24-32) [431]	12% (9-14) [881]
Patients who received a RBC transfusion: month 1 compared to month 4 Crude percent [N]	22% [462] vs. 3% [343]	5% [918] vs. 3% [749]
Patients who had a ≥ 3-point change in FACT-F score at week 16 Crude Percent (95% CI) [N]	58% (53-64) [303]	53% (49-57) [647]
Mean Q3W dose administered (95% CI)	331.1 mcg (325.8-336.3)	319 mcg (315.5-322.6)
Number of patients who had a dose increase (%)	207 (45%)	336 (37%)

^a Q3W = every three weeks, Hb = hemoglobin, CI = confidence interval, RBC = red blood cell, KM = Kaplan Meier estimation, NE = Not Estimable, EOS = end of study, FACT- F = Functional Assessment of Cancer Therapy-Fatigue subscale.

^b ≥ 11 g/dL

^c 11-13 g/dL

^d 2 g/dL Hb increase from baseline or > 12 g/dL in the absence of RBC transfusion within preceding 28 days

^e crude percent indicates actual number of patients

QW groups, 36 versus 43 days, respectively. Accounting for dosage adjustments, the average darbepoetin alfa dose for the Q3W group was 375 mcg [125 mcg QW] and the average dose for the QW group was 107.8 mcg.¹⁷

Epoetin Alfa

In clinical practice, epoetin alfa is usually administered weekly for the management of CIA.^{10,11} However, in recent years a limited number of studies have been conducted to investigate extended-dosing intervals to enhance convenience. Some of these studies have evaluated the use of front-loading (induction phase) or the administration of more frequent doses for a scheduled number of weeks or until a specific Hb level is reached.^{18,21-23} This induction phase is then followed by a maintenance phase in which the same or higher dose is administered at less frequent intervals.

A phase 3, open-label, comparative study in CIA published by *Steensma et al* enrolled 365 patients to initially receive epoetin alfa 40,000 units QW for 3 weeks (front-loading, initiation phase).¹⁸ Patients were then randomized to either continue this weekly regimen (n = 183) or receive 120,000 units Q3W (n = 182) for an additional 18 weeks (maintenance phase). Dose reductions, but not increases, were permitted. Eligible patients were anemic due to either a nonmyeloid cancer or chemotherapy, and concurrent chemotherapy treatments were not required. Results of the primary efficacy endpoint analysis, the proportion of patients who received a RBC transfusion, were comparable between groups for the entire study period [23% (QW) and 18% (Q3W), P = 0.22] as well as for the maintenance phase [13% (QW) and 15% (Q3W), P = 0.58]. However, in reviewing secondary endpoints,

patients enrolled into the QW group demonstrated a greater Hb response than the Q3W group including a slightly higher mean end of study Hb level (12.0 g/dL versus 11.5 g/dL, respectively; P = 0.0006) and a greater mean increase in Hb from baseline to last measured value (1.8 g/dL versus 1.4 g/dL, respectively; P = 0.01). Patients in the QW group were more likely to have a drug dose held due to Hb levels exceeding 13 g/dL. Adverse events, overall survival and QOL were similar between groups. Potential limitations of this study included a lack of blinding and a greater frequency of Hb assessments in the QW arm. Additional studies are required to further investigate the clinical benefits of this Q3W epoetin alfa regimen.

A randomized, open-label, 13-week study was conducted by *Henry et al* comparing 80,000 units of epoetin alfa Q2W with 40,000 units QW in anemic patients with nonmyeloid malignancies and planned chemotherapy for ≥ 12 weeks.¹⁹ Regimens were modified to maintain Hb levels at approximately 12 g/dL. The analysis of the primary efficacy endpoint, the mean Hb change from baseline to end of study, included 295 patients [N = 151 (Q2W); N = 141 (QW)]. Results for this endpoint were comparable between groups, 1.6 g/dL and 1.8 g/dL, Q2W versus QW, respectively (per-protocol population). The KM estimates for RBC transfusions from day 29 to the end of study were also similar between groups, 11.2% and 12.0%, Q2W versus QW, respectively. More patients in the QW required dose holds due to excessive Hb levels (> 13 g/dL) or dose reductions due to high Hb levels (> 12 g/dL) or a rapid rise in Hb (> 1 g/dL in any 2-week period). Thirteen percent of the patients in the Q2W group were switched to QW dosing due to an inadequate Hb response. The rate

of clinically relevant thrombovenous events [7.8% (Q2W) versus 7.6% (QW)] and deaths [6.5% (Q2W) versus 6.2% (QW)] were similar between groups. All deaths were determined to be unrelated to the study drug.

In addition to the studies presented here, other extended epoetin dosage regimens have been evaluated.²¹⁻²³ Although outcomes from these studies suggest positive outcomes in terms of hematologic response and RBC transfusion requirements, more research is warranted before the most effective and safe extended epoetin alfa regimen is determined.

ESP Administration Q3W: Convenient and Efficient Care

Cancer patients undergoing chemotherapy often schedule additional clinic visits for QW or Q2W ESP administration. Approximately 40 - 50% of chemotherapy is administered every three weeks or on 21-day cycle.¹⁰ The opportunity for patients to receive ESP therapy during scheduled chemotherapy clinic visits would be optimal for all involved. *Fortner et al* found that 83% of all patients required assistance with transportation to and from the clinic.²⁴ Patients and caregivers often need to take paid and unpaid time off from work to accommodate appointment times. Synchronizing the administration of ESP therapy with the scheduled chemotherapy can potentially minimize these disruptions as well as improve resource utilization in the clinics. The recent approval of the Q3W administration of darbepoetin alfa may assist in achieving these goals.

Chemotherapy regimens used to treat breast and other gynecologic cancers are often scheduled on a 21-day cycle.¹⁰ Women diagnosed with breast cancer, particularly those who are younger, are often more

likely to be working, active in the community, and are the primary caregivers for their families. The Q3W administration of an ESP would allow cycle-to-cycle dosing with added convenience for these patients. *Silberstein et al* separately reviewed patients with breast cancer who were enrolled in the previously described Synchronicity Trial (n = 354; 29% of all patients).^{16,25} Results of this subset analysis were comparable to those of the original trial, with 83% of patients achieving the target Hb level (≥ 11 g/dL) and 77% maintaining Hb levels within the target range (11-13 g/dL). In addition, Hb increases correlated with clinically significant improvements in QOL. *Glaspay et al* evaluated the efficacy of darbepoetin alfa 6.75 mcg/kg administered Q3W in anemic patients with breast cancer (n = 32) compared to all anemic cancer patients (n = 81) enrolled in the study.²⁶ The mean change in Hb from baseline until after week 6 of therapy was similar between patients with breast cancer (1.1 g/dL) compared to all patients (1.0 g/dL). Hematopoietic response rates (≥ 2 g/dL Hb increase

from baseline or Hb ≥ 12 g/dL) were also similar between groups, 78% and 74%, breast cancer patients versus all patients, respectively.

Erythropoietic stimulating proteins administered Q3W may also enhance economic outcomes for oncology clinics. A patient receiving a weekly ESP 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 ESP administration can be reduced and clinic resources redirected towards the administration of chemotherapy. Generally, the reimbursement for a growth factor injection is 1/20th of the reimbursement for chemotherapy administration.²⁷ Therefore, facilitating chemotherapy administration in lieu of growth factor injections is financially desirable to health systems. These operational efficiencies were validated by both *Beverage et al* and *Griffith et al* who found that the frequency of growth factor administration is significantly reduced when long-acting agents are utilized.^{28,29}

Conclusion

For the many cancer patients receiving cyclic chemotherapy, QW or Q2W ESP regimens may require additional clinic visits leading to further inconvenience for patients and caregivers as well as increased clinic resource utilization. With the recent FDA approval of darbepoetin alfa, 500 mcg Q3W, for the management of CIA, ESP therapy may be synchronized with 21-day cycle chemotherapy. However, it is important to note, in the phase 3 trial providing the basis for this new dosing recommendation, more than 70% of patients required a 40% dosage reduction resulting in an average Q3W dose of 375 mcg. This dose is more consistent with the findings of previous studies concluding that darbepoetin alfa, with a beginning dose of 300 mcg Q3W, is effective in the management of CIA.^{15,16} Extended epoetin alfa regimens are currently under investigation and may provide additional extended ESP dosing alternatives.

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