Hosp Pharm 2013;48(2):120–126

www.thomasland.com
doi: 10.1310/hpj4802-120

Original Article

Erythropoiesis-Stimulating Agent (ESA) Practice Patterns in Patients With Chemotherapy-Induced Anemia (CIA) Treated at Hospital Oncology Clinics

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Abstract

Objectives: To characterize erythropoiesis-stimulating agent (ESA) usage initiated in hospital outpatient oncology centers that employ weekly (QW) and every-3-week (Q3W) ESA dosing regimens; describe the frequency of ESA dosing, transfusions, hemoglobin determinations, and anemia-related visits between these 2 regimens; and compare the rates at which inpatient ESA doses are administered on QW versus Q3W schedules.

Methods: This was a retrospective, observational record review evaluating ESA usage in 641 patients from 8 outpatient oncology clinics throughout the United States. Adult patients who initiated myelosuppressive chemotherapy for a documented solid tumor between August 1, 2007 and June 30, 2009 and received their first 3 consecutive outpatient ESA doses on a QW or Q3W schedule were eligible for study inclusion. During a single course of chemotherapy, ESA administrations were recorded as long as ESA therapy was continued on the initial regimen. ESA doses were captured until termination of ESA therapy, until 9 months had elapsed since the first ESA dose, until the patient was switched to another ESA regimen, or until death. ESA administration during inpatient admissions was also recorded.

Results: ESA utilization varied between the dosing groups, with fewer ESA doses administered per follow-up month in patients receiving Q3W versus QW ESA therapy (mean, 1 vs 2 doses). Compared to weekly administration, extended-dose ESA therapy also reduced the number of hemoglobin determinations and anemia-related visits without chemotherapy required per follow-up month. Neither the number of transfusions nor the number of packed red blood cell units administered per follow-up month differed between treatment groups. Compared to weekly ESA therapy, Q3W administration reduced costs associated with ESA prescribing and utilization.

Conclusion: Extended-dose ESA therapy (Q3W dosing) may improve practice efficiency and may be associated with reduced frequencies of hemoglobin determinations and ESA doses required. Q3W dosing may also reduce inpatient ESA utilization by reducing the number of ESA doses required for previously maintained outpatients.

Key Words—anemia, erythropoiesis-stimulating agents, ESA, inpatient, outpatient

Hosp Pharm—*2013;48(2):120–126*

Affecting an estimated 70% to 90% of patients receiving myelosuppressive chemotherapy, anemia is a serious and often debilitating side effect related to cancer treatment.[1] Characterized by reduced hemoglobin (Hgb) and hematocrit (Hct) levels, chemotherapy-induced anemia (CIA) can cause significant fatigue and may have a profound impact on physical and psychosocial function.[1] Erythropoiesis-stimulating agents (ESAs) (ie, epoetin alfa [EA], darbepoetin alfa [DA]) are treatment options for management of CIA in the noncurative setting. ESA treatment in patients with non-curative, non-myeloid

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malignancy and CIA is used, where clinically appropriate, to alleviate anemia-related symptoms.[2-4] The risks and benefits of ESA use continue to be evaluated through the US Food and Drug Administration (FDA)–mandated Risk Assessment and Mitigation Strategy program APPRISE.[5]

Both EA and DA are FDA approved for the treatment of anemia due to the effects of concomitant myelosuppressive chemotherapy. Upon initiation, there is a minimum of 2 additional months of planned chemotherapy. EA is a short-acting agent with a recommended dosing interval of at least once a week (QW), whereas DA is a unique molecule that was approved for every-3-week (Q3W) dosing in 2006.[6,7] The recommended starting dose of EA is 150 units/kg 3 times per week or 40,000 units QW, whereas DA may be dosed at 2.25 mcg/kg QW or 500 mcg Q3W.[8,9] Current labeling stipulates that ESA therapy may be initiated in chemotherapy patients if they have a hemoglobin (Hgb) level less than 10 g/dL and the lowest dose that is needed to avoid transfusion should be used.[6,7,9] In July 2007, the Centers for Medicare and Medicaid Services (CMS) enacted a National Coverage Decision restricting ESA therapy to Hgb levels less than 10 g/dL, limiting treatment duration to a maximum of 8 weeks following cessation of chemotherapy, and limiting ESA starting doses to those recommended by the FDA.[10]

The introduction of long-acting ESA therapy has impacted ESA usage patterns. Some facilities have switched to Q3W DA dosing following approval of this regimen in 2006, while others have continued to dose DA once weekly.[11] Previous studies have demonstrated improvements in practice efficiency when DA is administered at extended dosing intervals as opposed to once weekly.[12,13] The use of extended dosing has been shown to reduce patient visits and reduce staff time devoted to routine anemia management.[12,13] This study was designed to characterize ESA usage initiated in hospital outpatient oncology centers that employ QW and Q3W ESA dosing regimens and to describe the frequency of ESA dosing, transfusions, Hgb determinations, and anemia-related visits associated with these 2 regimens.

The use of long-acting ESAs in the hospital outpatient setting may reduce the need for inpatient doses, as many patients are adequately covered throughout their stay by their most recent outpatient ESA dose.[14] To assess this, an exploratory objective of this study was to compare rates at which inpatient ESA doses are administered to patients receiving ESAs on QW versus Q3W schedules.

METHOD

Subjects and Study Design

This was a retrospective, observational record review evaluating ESA usage in 8 outpatient oncology clinics throughout the United States. All sites were owned by, or affiliated with, a hospital or health system, allowing for assessment of both outpatient and inpatient ESA use among study patients. Eligible clinics utilized ESAs for the treatment of CIA on QW and Q3W schedules and were able to provide data describing up to 50 patients per regimen. In addition, clinics had to confirm that they did not dictate usage of a particular ESA regimen based on patient demographics, tumor type, chemotherapy regimen, or other clinical parameters.

Adult patients who initiated myelosuppressive chemotherapy for a documented solid tumor (ie, breast, lung, gastrointestinal, uterine, cervical, ovarian, lymphoma, or other solid tumor) between August 1, 2007 and June 30, 2009 were eligible for inclusion in the study. This time period was selected because it was after the last reimbursement coverage decision following the implementation of the National Coverage Decision for ESA use in CIA. In addition, all subjects had to receive their first 3 consecutive outpatient ESA doses in the clinic on a QW or Q3W schedule in order to verify that they were being dosed on the given regimen. They also had to have electronic or paper medical records available to describe chemotherapy and anemia management, so investigators would be aware of valid reasons for ESA dose delays. Eligible patients could only be included in the study a single time; in the event that a subject initiated multiple courses of ESA therapy during the study period, only the first course was considered for analysis. Patients were excluded from analysis if they had a recorded history of myelodysplastic syndrome (MDS) or anemia of cancer, were receiving alternative ESA regimens, were receiving an ESA as part of an investigational protocol, were previously entered into the study, and did not have adequate records.

Patients meeting inclusion were assigned to 1 of 2 groups: those initiating therapy on a QW schedule (ie, had their first 3 ESA doses separated by 5 to 9 days), and those initiating therapy on a Q3W schedule (ie, had their first 3 ESA doses separated by 19 to 23 days). Patient inclusion was continued until 50 subjects were included in each group (ie, 100 subjects from each clinic) or until all eligible patient records were exhausted.

ESA therapy administered during a single course of chemotherapy was included in analysis. A course of

chemotherapy was defined as a series of consecutive cycles of any myelosuppressive chemotherapy regimen intended to treat a solid tumor, preceded by at least 90 days without any chemotherapy and followed by at least 90 days without chemotherapy. Within this interval, patient records were monitored as long as ESA therapy was continued on the initial regimen or longer if a valid reason for dose delay was noted (ie, postponement of chemotherapy, elevated Hgb level, hospitalization, recent transfusion, other documented administrative or clinical events such as office closure or patient illness). ESA doses were captured until termination of ESA therapy (defined as a 42-day gap since the previous dose), until 9 months had elapsed since the first ESA dose, until the patient was switched to another ESA regimen, or until death. In addition to ESA-related information, the following demographics were recorded for all patients included in the study: age, gender, race, insurer, primary tumor site, presence of metastatic disease, and class of chemotherapy administered (ie, antimitotics, platinum compounds, antimetabolites, antibiotics, non-platinum-containing alkylating agents, other).

Outcome Measures

The following outcome measures were evaluated in the outpatient ESA utilization analysis and were compared between patients receiving QW versus Q3W administration regimens: number of ESA doses per follow-up month, mean pre-ESA administration Hgb value, number of ESA micrograms or international units per follow-up month, number of Hgb determinations per follow-up month, number of packed red blood cell (PRBC) transfusions per follow-up month, number of PRBC units per follow-up month, number of anemia-related visits with chemotherapy per follow-up month, number of anemia-related visits without chemotherapy per follow-up month, duration of follow-up, and reason for termination of follow-up. Measures per follow-up month were calculated by dividing the number of units (ie, ESA doses, ESA micrograms/international units, Hgb determinations, PRBC transfusions, PRBC units, anemia-related visits) by the number of months the patient was observed. For simplicity, each consecutive 30-day period was considered to be 1 month.

A secondary analysis was conducted to examine the association between extended ESA dosing and inpatient ESA administration. To compare ESA utilization between the 2 outpatient dosing schedules, investigators evaluated and compared the number of patients on each regimen who received 1 or more ESA doses during an inpatient stay as well as the number of ESA doses administered per follow-up month; individual hospitalizations were considered separately for this analysis (ie, each patient could be evaluated more than once).

ESA drug acquisition costs were not included in any of the site or regimen data collection or analyses.

Statistical Analysis

According to the ESA labels and previous research, the most frequent dose was 500 mcg per administration for Q3W ESAs, 200 mcg per administration for Q2W ESAs, and 40,000 units per administration for QW.[11] Assuming the most frequent doses are the average doses for each regimen, the calculated 95% CIs for each regimen are presented in **Table 1**. This table shows that with a sample size equal to 500 for each arm, we will have 95% CI width less than 15% of the mean estimations.

Baseline characteristics of QW and Q3W groups were compared using the Student's *t* test (for age) and chi-square test (all other measures). The monthly frequency of ESA doses, ESA units, Hgb determinations, PRBC transfusions, PRBC units, anemia-related visits with chemotherapy, anemia-related visits without chemotherapy, and the duration of follow-up were compared, with the unit of analysis being an individual patient.

Comparisons were made using Student's *t* test (when the endpoint was normally distributed) or Wilcoxon

Table 1. Calculated 95% CI for each erythropoieses-stimulating agent regimen (n = 500)

Regimen	Mean	SD	Lower 95% CI	Upper 95% CI	CI Width/Mean
Q2W	100.0	53.0	95.4	104.6	9%
Q3W	166.7	88.3	158.9	174.4	9%
QW	40000.0	32800.0	37125.0	42875.0	14%
QW (DCR 326:1)	122.7	100.6	113.9	131.5	14%

Note: DCR = dose conversion rate of erythropoietin alfa to darbepoietin in mcg; QW = once a week; Q3W = once every 3 weeks.

rank sum (if not normally distributed); these allow for comparisons between small-sized, differently sized patient groups. Mean pre-ESA Hgb level was compared using Student's *t* test, with the unit of analysis being an individual ESA dose. Reason for termination of follow-up was compared using chi-square, with the unit of analysis being an individual patient. The proportion of patients receiving at least 1 inpatient ESA dose was compared using chi-square. The number of inpatient ESA doses per follow-up month was compared using Wilcoxon rank sum.

RESULTS

A total of 641 patients were included in the study; 195 patients received weekly ESA therapy (1,512 doses) while 446 patients were dosed every 3 weeks (1,358 doses). **Table 2** illustrates baseline patient demographics. The majority of subjects were Caucasian and female, and, on average, patients were in their early 60s. There were no significant differences in age or gender between groups, but more patients receiving QW versus Q3W therapy were Caucasian. Primary insurance coverage also differed significantly between groups. The most commonly involved tumor sites were breast, lung, and other. ESA dosing regimens differed significantly between certain tumor sites (eg, lung, gastrointestinal, ovarian, other), but not between others. A greater number of patients receiving QW ESA therapy had metastatic disease compared to those on a Q3W regimen. Finally, the most commonly utilized chemotherapeutic medications included antimitotics and platinum compounds; overall, medication use differed significantly between groups.

Table 3 details data from each of the outpatient ESA utilization outcome measures. Mean follow-up duration was longer among patients dosed every 3 weeks compared to those who were dosed weekly (136 vs 122 days). Reasons for termination of follow-up differed between treatment groups, but the most common reason was termination of ESA therapy (ie, 42 days since previous dose was administered).

ESA dosing frequency varied significantly between treatment groups, with fewer ESA doses administered per follow-up month in patients receiving Q3W versus QW ESA therapy (1 vs 2 doses). In addition, while the mean pre-ESA-administration Hgb level was statistically significantly different between treatment groups (9.7 vs 9.6 g/dL for Q3W and QW regimens, respectively), it was most likely not clinically significant. The mean number of micrograms of DA administered per follow-up month also varied between groups, with a greater quantity administered to patients receiving Q3W ESA therapy (406 vs 212 mcg for Q3W and QW regimens, respectively). Fewer Hgb determinations were needed per follow-up month in patients receiving Q3W versus QW therapy (3.1 vs 4.0 determinations).

Neither the number of transfusions nor the number of PRBC units administered per follow-up month differed between treatment groups (0.16 transfusions and 0.31 units vs 0.17 transfusions and 0.30 units for Q3W and QW regimens, respectively). Nevertheless, significantly fewer anemia-related visits without chemotherapy were required per follow-up month in patients receiving Q3W versus QW ESA therapy (1.6 vs 2.4); however, anemia-related visits with chemotherapy did not differ between groups.

Table 2. Patient demographics

Demographics	QW (n=195)	Q3W (n=446)	*P* value[a]
Mean age, years (SD)	62 (13)	62 (12)	.45
Gender			.24
Female	135 (69)	329 (74)	
Race			<.01
Caucasian	144 (74)	268 (61)	
Insurer			<.01
Government	119 (61)	215 (48)	
Private	61 (31)	205 (46)	
Uninsured/Unknown	15 (8)	26 (6)	
Tumor site			
Breast	45 (23)	97 (22)	.71
Lung	53 (27)	81 (18)	<.01
Gastrointestinal	8 (4)	17 (4)	.86
Uterine	4 (2)	32 (7)	<.01
Cervical	5 (3)	18 (4)	.36
Ovarian	14 (7)	74 (17)	<.01
Lymphoma	14 (7)	15 (3)	.03
Other	59 (30)	131 (29)	.82
Presence of metastasis	145 (74)	282 (63)	<.01
Chemotherapy			
Antimitotics	101 (52)	270 (61)	.04
Platinum compounds	97 (50)	260 (58)	.04
Antimetabolites	76 (39)	126 (28)	<.01
Antibiotics	43 (22)	64 (14)	.02
Alkylating agents	35 (18)	78 (17)	.89
Other	91 (47)	212 (48)	.84

Note: Values are given as n (%) unless otherwise indicated. QW = once a week; Q3W = once every 3 weeks.
[a]Student's *t* test (for age) and chi-square test (for all other measures).

Table 3. Outpatient ESA utilization outcome measures*

Outcome measure	QW (n=195)	Q3W (n=446)	*P* value*
No. of ESA doses per F/U month	2.0 (0.8)	1.0 (0.2)	<.01
Pre ESA administration Hgb level (g/dL)	9.6 (1.0)	9.7 (1.0)	<.01
ESA units per F/U month			
EA (IU)	40 k (52 k)	0 k (1 k)	<.01
DA (mcg)	212 (239)	406 (128)	<.01
No. of Hgb determinations per F/U month	4.0 (1.8)	3.1 (1.7)	<.01
No. of PRBC transfusions per F/U month	0.17 (0.36)	0.16 (0.34)	.80
No. of PRBC units per F/U month	0.30 (0.64)	0.31 (0.63)	.87
No. of anemia-related visits with chemotherapy per F/U month	1.7 (1.2)	1.6 (0.9)	.25
No. of anemia-related visits without chemotherapy per F/U month	2.4 (1.8)	1.6 (1.5)	<.01
Duration of F/U, days	122 (68)	136 (47)	.01
Reason for termination of F/U, n (%)			<.01
Death	39 (20)	21 (5)	
9 months elapsed	7 (4)	7 (2)	
42 days between doses	126 (65)	393 (88)	
Change in regimen	9 (5)	11 (2)	
Lost to F/U	14 (7)	14 (3)	

Note: Values given as mean (SD) unless otherwise indicated. DA = darbepoetin alfa; EA = epoetin alfa; ESA = erythropoiesis-stimulating agent; F/U = follow-up; Hgb = hemoglobin; IU = international units; PRBC = packed red blood cells; QW = one time per week ESA administration; Q3W = one time every 3 week ESA administration.
*P values were determined using Student's t test (or Wilcoxon rank sum data if not normally distributed).

As shown in **Table 4**, extended ESA dosing was associated with a reduction in inpatient ESA utilization. Inpatient ESA utilization was very low relative to the entire study population. A smaller percentage of patients who were dosed Q3W received 1 or more inpatient ESA doses compared to those dosed QW (4.3% vs 11.8%).

DISCUSSION

This retrospective, observational record review evaluated and compared commonly employed ESA dosing regimens from August 1, 2007 to June 30, 2009 among patients with CIA who were receiving myelosuppressive chemotherapy for solid tumor malignancies. Compared to weekly therapy, extended-dose ESA regimens were associated with a decrease in monthly outpatient dosing frequency, as well as a reduction in the number of Hgb determinations and anemia-related visits without chemotherapy required per follow-up month. These data indicate that extended-dose ESA therapy has the potential to improve practice efficiency by reducing clinic workload, decreasing patient burden, and saving staff time. Compared to weekly dosing, extended-dose therapy was associated with a reduction in inpatient ESA utilization among previously maintained outpatients.

These findings are consistent with previous research, which indicates that extended-dose ESA therapy improves practice dynamics by reducing dosing frequency and saving time, both for patients and for clinic personnel. Specifically, one time and motion study comparing weekly ESA administration with extended-

Table 4. Inpatient ESA utilization outcome measures

Outcome measure	QW (n=195)	Q3W (n=446)	*P* value*
No. of patients receiving 1 or more inpatient ESA doses (%)	23 (11.8)	19 (4.3)	<.01
Mean number of inpatient ESA doses per F/U month (SD)	0.05 (0.16)	0.01 (0.06)	<.01

Note: ESA = erythropoiesis-stimulating agent; F/U = follow-up; QW = one time per week ESA administration; Q3W = one time every 3 week ESA administration.
*P values were determined using Student's t test (or Wilcoxon rank sum data if not normally distributed).

dose DA administration found that long-acting therapy reduced ESA dosing frequency by 48%, resulting in significant time savings and improving quality of life, both among patients and clinic staff.[11] Another study comparing weekly ESA therapy with long-acting therapy found that long-acting therapy decreased ESA dosing frequency by 38% and, as such, reduced the mean number of required clinic visits by 23%.[13] The present study is consistent with these results. This is an important finding, as Q3W DA dosing has been on the rise since its approval in 2006. As an estimated 40% of oncology patients receive chemotherapy on a 21-day cycle, Q3W DA administration may be synchronized with chemotherapy, thereby reducing clinic visits and redirecting clinic resources to other vital issues.[15]

Although this study provides important insights regarding ESA practice patterns, there are several potential limitations that must be taken into consideration. First, the study was initiated during the time when the National Coverage Decision as well as the Risk Evaluation and Mitigation Strategies for ESAs were being created and implemented,[9,15] which could have, knowingly or unknowingly, impacted clinician practice during study. This could not be assessed by the investigators. Second, several baseline characteristics (race, insurance coverage, tumor site, chemotherapy, metastasis) differed significantly between groups, which may have affected study outcomes. However, clinics did have to confirm that they do not dictate usage of a particular ESA regimen based on patient demographics, tumor type, guidelines that make recommendations based on chemotherapy regimen, or other clinical parameters. The specificity of internal institutional guidelines for ESA use, and the rigor with which they are enforced, was outside the control of this investigation. Thus, guidelines within a particular institution may not have been strictly enforced; moreover, guidelines may have differed between institutions. Another potential limitation impacting the data analysis in this study is the difference in the sample size between the 2 groups (195 vs 446). Even when the data were re-analyzed excluding the top 5% of utilizers, we found the results to be essentially unchanged. Also, although the QW and Q3W groups were not completely balanced on the basis of race, tumor sites, or insurance, we found no important relationship between these potentially confounding factors and utilization rates. In addition, study findings may not be generalizable to patients or clinics that vary from those included in this analysis. For instance, outcome measures may differ among patients who received fewer than 3 ESA doses per course or among oncology clinics with dissimilar characteristics (eg, those that are not affiliated with a hospital or health care system). Finally, the secondary inpatient analysis could have been more detailed in order to obtain more accurate results. In addition, while investigators compared ESA use between the 2 outpatient regimens, the study methodology did not allow for determination of whether an inpatient dose was actually due. The appropriateness of inpatient ESA therapy could have been better assessed by comparing ESA use among those in whom a dose was due versus those in whom it was not. As a result, no conclusions can be made relative to inpatient ESA use evaluation, and this remains a subject for future evaluation.

In conclusion, the results of this study suggest that extended-dose therapy used in clinical practice may reduce staff and patient burden for clinic visits to receive ESA administrations, but subsequent studies should be conducted to better assess the impact of synchronizing ESA administration with chemotherapy on practice efficiency. Future studies to better analyze the impact of ESA dosing on inpatient administration and to evaluate the influence of ESA regimen on Hgb levels throughout the course of therapy should be conducted.

ACKNOWLEDGMENTS

John Reitan is a principle in the RJM Group LLC, which has received research support from Amgen. Patricia Corey-Lisle, Sanatan Shreay, and Ze Cong are employees of Amgen. Arletta van Breda contracted with RJM Group LLC to coordinate data collection.

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