Original Article

Benefits Associated with an Early Hemoglobin Response to Epoetin Alfa Therapy in the Treatment of Chemotherapy-Related Anemia

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Key Words

Epoetin alfa, early hemoglobin response, blood transfusion, quality of life, drug utilization, chemotherapy-related anemia

Abstract

Although previous studies have recognized that timely correction of anemia is desirable, no published research quantifies the association between the timeliness of the hemoglobin rise and patients' outcomes. This study evaluates whether anemic patients with cancer who are receiving chemotherapy and who experienced an early response to epoetin alfa (≥ 1 g/dL hemoglobin increase at the end of 4 weeks of treatment) experienced better clinical and drug utilization outcomes compared with patients who did not experience an early response. Three large, open-label, community studies of epoetin alfa for the treatment of chemotherapy-related anemia were retrospectively analyzed to assess the association of early hemoglobin response to subsequent transfusion requirements, subsequent hemoglobin response, quality of life, and epoetin alfa dosage administered over the study. Two epoetin alfa dosing regimens were evaluated: 10,000 units 3 times weekly with potential escalation to 20,000 units, and 40,000 units once weekly with potential escalation to 60,000 units. In all studies, patients who experienced an early hemoglobin response had statistically lower subsequent transfusion requirements, higher rates of subsequent hemoglobin response, shorter time to hemoglobin response, better improvements in quality of life scores, and lower average weekly epoetin alfa dose than patients who did not experience an early hemoglobin response. Similar proportions of patients experienced early response in the 3-times weekly and once-weekly epoetin alfa regimens. This ad hoc analysis found that early hemoglobin response to epoetin alfa therapy was associated with improved clinical benefits and drug utilization. Early hemoglobin response may therefore be considered as a desired goal of epoetin alfa therapies. (*JNCCN* 2005;3:807–816)

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Submitted December 23, 2004; accepted for publication August 19, 2005.

This research was funded by Ortho Biotech Clinical Affairs, LLC (Bridgewater, NJ). Dr. Duh, Mr. Lefebvre, and Dr. Rosberg are employed by Analysis Group, which has research contracts with Ortho Biotech Clinical Affairs. Dr. Campos has a consulting contract with Analysis Group. None of the authors have individual conflicts of interest.

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Anemia is a frequent complication of cancer and its treatment. A review of 1,064 patients with various types of cancer receiving non-platinum chemotherapy found that 37.1% of patients had a baseline hemoglobin (Hb) less than or equal to 12 g/dL, and that the prevalence of anemia increased to 54.1% after 3 cycles of chemotherapy.[1] Anemic patients typically experience debilitating symptoms such as fatigue, shortness of breath, and impaired functional status.[2] Fatigue is one of the most commonly reported signs in patients with cancer and has been associated with poor quality of life (QOL).[3–5] Recent research reported that fatigue manifests itself rapidly during the first 4 days from the onset of chemotherapy and continues for at least 90 days after treatment is completed.[6–8]

Previous studies have shown that erythropoietic agents are effective at alleviating anemia in patients with cancer while reducing transfusion requirements and improving patient QOL.[9–14] Researchers have also suggested that patients who responded early to epoetin alfa therapy subsequently experienced a meaningful Hb response, defined as an increase in Hb level of 2 g/dL or

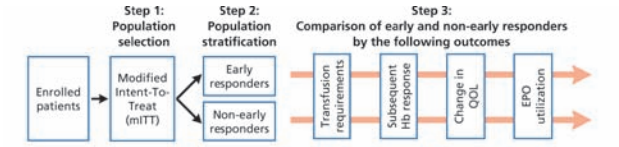
greater or the attainment of an Hb level of at least 12 g/dL by the study end.[9,15]

Recent multicenter observational studies have reported an average treatment duration of 8 to 10 weeks for erythropoietic agents,[16–19] which highlights the need for effective and timely hematologic improvement. Thus far, no study has assessed the potential benefits of an early response to erythropoietic therapies in patients with chemotherapy-related anemia. Benefits of early treatment response for anemia have not received the same attention as benefits of early treatment response in other conditions, such as pain, migraine, nausea, and vomiting. In these conditions, early intervention and treatment have been shown to have positive outcomes.[20,21] This study assesses whether an early Hb response is associated with lower blood transfusion requirements, higher subsequent Hb response, greater improvement of QOL, and lower overall erythropoietic drug utilization in anemic patients receiving chemotherapy or radiotherapy.

Patients and Methods

Design of the Original Studies

We retrospectively analyzed data from 3 prospective, multicenter, single-arm, open-label epoetin alfa trials, including one with a 3-times weekly dosing regimen (TIW study)[9] and 2 with a once-weekly dosing regimen (QW studies 1 and 2).[10,14] These studies enrolled a total of 6,159 patients: 2,370 from the TIW study; 3,012 from QW study 1, and 777 from QW study 2 (Figure 1). The studies prospectively evaluated the efficacy of epoetin alfa therapy over 16 weeks in patients receiving chemotherapy alone or in combination with radiotherapy. Patients were enrolled if they were 18 years old or older, had a life expectancy of 6 months or more, had an Hb level 11.0 g/dL or less, and had a non-myeloid malignancy and were receiving chemotherapy alone or concomitantly with radiotherapy (QW study 2). Patients were excluded if they had anemia attributable to other factors, such as hemolysis, gastrointestinal bleeding, or iron or folate deficiency; received epoetin alfa therapy in the past 3 months; were candidates for bone marrow transplantation; or were receiving peripheral blood progenitor cell therapy. Stage of cancer was not a criterion. All patients provided written informed consent.



Study	Number of patients enrolled	Analytical approach	Number of early responders (%) / Non-early responders (%)	Based on patients on study beyond Week 4: Subsequent transfusion requirements	Based on patients on study beyond Week 4: Subsequent Hb response	Change in QOL scores	EPO utilization
TIW Study	2,370	OT, *n* = 1,860	963 (51.8) / 897 (48.2)	*n* = 1,655	*n* = 1,655	Wk 8:*N* = 1,477 EOS:*N* = 1,516	*n* = 1,858
		LVCF, *n* = 2,043	987 (48.3) / 1,056 (51.7)	N/A	N/A	Wk 8:*N* = 1,987 EOS:*N* = 1,987	N/A
QW Study 1	3,012	OT, *n* = 2,454	1,157 (47.1) / 1,297 (52.9)	*n* = 2,198	*n* = 2,198	Wk 8:*N* = 1,760 EOS:*N* = 1,996	*n* = 2,444
		LVCF, *n* = 2,677	1,182 (44.2) / 1,495 (55.8)	N/A	N/A	Wk 8:*N* = 2,642 EOS:*N* = 2,642	N/A
QW Study 2	777	OT, *n* = 607	297 (48.9) / 310 (51.1)	*n* = 566	*n* = 566	Wk 8:*N* = 445 EOS:*N* = 504	*n* = 607
		LVCF, *n* = 638	307 (48.1) / 331 (51.9)	N/A	N/A	Wk 8:*N* = 633 EOS:*N* = 633	N/A

Figure 1 Analytic steps and population sample size. EPO, epoetin alfa; EOS, end of study; OT, on-treatment; LVCF, last value carried forward; QOL, quality of life.

For the TIW study, patients received epoetin alfa 10,000 units subcutaneously 3 times weekly, with an increase to 20,000 units if the Hb level had not increased by at least 1 g/dL over baseline after 4 weeks of therapy. In both QW studies, patients received an initiation dose of epoetin alfa 40,000 units/wk subcutaneously with dose escalation to 60,000 units weekly if the Hb response was inadequate (Hb level rise < 1 g/dL over baseline after 4 weeks of therapy). At any point during either study, if a patient's Hb level rose above 13 g/dL, epoetin alfa therapy was stopped until the Hb level decreased to 12 g/dL and then resumed at 75% of the original dose. The dose was also reduced if Hb increased more than 1.3 g/dL in a 2-week period.

Clinical and drug utilization outcomes were assessed over 16 weeks. Hb levels were measured every 4 weeks. Transfusions were recorded as they occurred. Patient-perceived QOL measurements were administered at baseline, week 8, and at the date patients completed or stopped participating in the study. In all 3 studies, patients were asked to rate their energy level, ability to perform daily activities, and overall QOL using a Linear Analog Scale Assessment (LASA, 100-mm) for each item. For the TIW study and QW study 1, patients' QOL was also evaluated using the anemia (FACT-An) and fatigue (FACT-F) subscales of the Functional Assessment of Cancer Therapy (FACT) questionnaire.[22]

Design of Current Analysis

Statistical analyses were performed on the modified intent-to-treat (mITT) population. The mITT population consisted of all patients who met inclusion and exclusion criteria and who received at least one

dose of the study medication. Patients who experienced an early Hb response after 4 weeks of epoetin alfa therapy but who had also received a red blood cell transfusion within 28 days before the response were further excluded to avoid attributing an early response to transfusions.

Data were analyzed with 2 methods—last value carried forward (LVCF) and on-treatment (OT)—to assess the robustness of the results. The LVCF approach imputed missing data by carrying forward the last observed value of the endpoint considered. The OT approach analyzed data as they were available without imputing missing values. As a result, the sample size available for the OT analysis varied over time points and across outcomes of interest. Moreover, patients missing the Hb value at week 4 were excluded from the OT analysis because investigators could not determine whether they experienced early response.

Analyses of association between early response and QOL were conducted using both LVCF and OT approaches, whereas the analyses on subsequent blood transfusions, subsequent Hb response, and epoetin alfa drug utilization were conducted using the OT approach only.

A retrospective cohort design was used to study the effect of early Hb response on various outcomes of interest. As described in Figure 1, an mITT population selected from all enrolled patients was stratified into 2 cohort groups: early responders and non-early responders. Patients were considered to be early responders if their Hb level was 1 g/dL or more over baseline at the end of the fourth week of epoetin alfa treatment and if they did not receive any packed erythrocyte transfusions in the 28 days before the week-4 Hb assessment. The remaining patients were defined as non-early responders, regardless of whether they responded later in the study (Figure 1).

The numbers of patients available for analysis varied for different outcomes. For analysis of subsequent transfusion requirements and subsequent Hb response, only patients who remained on study beyond week 4 were included. To be included in the LVCF and OT analyses of change in QOL scores, patients had to have the baseline QOL score and the baseline plus at least one more QOL score at week 8 or 16, respectively. For the epoetin alfa utilization outcome, data from patients with non-missing epoetin alfa dosage information were used for analysis. Data from the 3 studies were not pooled, and results from each study were reported separately.

The following clinical outcomes were investigated to compare the early response and non-early response groups: 1) proportion of patients receiving subsequent red blood cell transfusions between the end of week 4 and end of study; 2) subsequent Hb response between the end of week 4 and end of study for which subsequent Hb response was defined as a rise in Hb of 2 g/dL or more over baseline without a red blood cell transfusion in the preceding 28 days; 3) time to reach the subsequent Hb response between the end of week 4 and end of study; and 4) improvements in QOL scores at week 8 and end of study. Drug utilization outcome was calculated as the average weekly epoetin alfa dose during the treatment course.

Univariate and multivariate analyses were used to compare clinical and drug utilization outcomes of early responders and non-early responders for each study. Multivariate analysis of change in QOL was used to control for potential confounding factors that may have uneven distributions between early and non-early responders. Potential confounding factors included in this analysis were age, gender, tumor type, baseline Eastern Cooperative Oncology Group (ECOG) performance status (not available for the TIW study), baseline QOL score, tumor response, and change in Hb level between weeks 4 and 8 or end of study. Hemoglobin changes after week 4 were included in the regression models to isolate the effect of early Hb change on QOL improvement, rather than to control for uneven distribution of Hb change values between early and non-early responders. In addition to these factors, a binary variable to indicate if the patient received platinum chemotherapy was included in the analysis of QOL change at end of study, because the baseline risk for anemia is higher in patients receiving platinum-based chemotherapy than in those receiving non-platinum-based chemotherapy and epoetin alfa shows a stronger effect in patients receiving platinum-based chemotherapy.[23,24]

A sensitivity analysis evaluating the association between Hb change after 4 weeks of therapy, a continuous variable, and the clinical and drug utilization outcomes was also conducted. All statistical analyses were performed using SAS release 8.00 or newer (SAS Institute, Inc., Cary, NC).

Table 1 Baseline Characteristics for Early Responders and Non-Early Responders

	TIW Study			QW Study 1			QW Study 2		
Characteristics	Early Responders (*N* = 963)	Non-Early Responders (*N* = 897)	*P* value	Early Responders (*N* = 1,157)	Non-Early Responders (*N* = 1,297)	*P* value	Early Responders (*N* = 297)	Non-Early Responders (*N* = 310)	*P* value
Age, mean ± SD (years)	63.9 ± 13.1	62.6 ± 12.7	*P* = .0332	63.2 ± 13.0	63.0 ± 12.6	*P* = .7512	61.7 ± 12.7	61.7 ± 12.5	*P* = .9664
Gender, n (%)									
Female	607 (63.0%)	522 (58.2%)	*P* = .0328	780 (67.4%)	793 (61.1%)	*P* = .0012	178 (59.9%)	182 (58.7%)	*P* = .7591
Male	356 (37.0%)	375 (41.8%)		377 (32.6%)	504 (38.9%)		119 (40.1%)	128 (41.3%)	
Baseline Hb, mean ± SD (g/dL)	9.3 ± 1.0	9.5 ± 1.0	*P* = .0027	9.5 ± 0.9	9.6 ± 0.9	*P* = .0003	9.9 ± 0.9	10.1 ± 0.7	*P* = .0069
Baseline QOL[a] mean ± SD									
LASA Overall	46.8 ± 24.0	46.5 ± 24.2	*P* = .8232	48.6 ± 23.8	47.0 ± 23.1	*P* = .1093	48.1 ± 25.0	45.5 ± 25.3	*P* = .2125
LASA Energy	39.8 ± 21.6	39.9 ± 22.0	*P* = .8915	41.2 ± 21.2	39.5 ± 21.2	*P* = .0518	43.9 ± 22.5	39.7 ± 21.5	*P* = .0195
LASA Activity	40.5 ± 24.2	39.6 ± 24.1	*P* = .4400	43.3 ± 24.4	40.9 ± 23.3	*P* = .0119	42.7 ± 25.4	41.0 ± 24.7	*P* = .4020
FACT-An	42.4 ± 16.1	42.0 ± 15.9	*P* = .5771	43.9 ± 14.6	42.9 ± 15.1	*P* = .0933	N/A	N/A	
FACT-F	24.6 ± 12.6	24.5 ± 12.5	*P* = .8767	26.0 ± 11.4	25.3 ± 11.6	*P* = .1041	N/A	N/A	
Tumor Type, n (%)									
Breast	177 (18.4%)	140 (15.6%)	*P* = .0163	235 (20.3%)	238 (18.4%)	*P* = .0134	69 (23.2%)	45 (14.5%)	*P* = .0159
CLL	19 (2.0%)	20 (2.2%)		15 (1.3%)	21 (1.6%)		0 (0%)	1 (0.3%)	
Gastrointestinal	78 (8.1%)	96 (10.7%)		205 (17.7%)	174 (13.4%)		70 (23.6%)	56 (18.1%)	
Genitourinary	N/A	N/A		54 (4.7%)	74 (5.7%)		10 (3.4 %)	10 (3.2%)	
Gynecologic	144 (15.0%)	95 (10.6%)		152 (13.1%)	163 (12.6%)		15 (5.1%)	26 (8.4%)	
Hodgkin's Disease	21 (2.2%)	18 (2.0%)		18 (1.6%)	9 (0.7%)		1 (0.3%)	0 (0%)	
Lung	209 (21.7%)	225 (25.1%)		275 (23.8%)	346 (26.7%)		108 (36.4%)	126 (40.7%)	
Multiple Myeloma	66 (6.9%)	58 (6.5%)		47 (4.1%)	63 (4.9%)		1 (0.3%)	2 (0.7%)	
Non-Hodgkin's Lymphoma	88 (9.1%)	89 (9.9%)		90 (7.8%)	119 (9.2%)		4 (1.4%)	5 (1.6%)	
Other	156 (16.2%)	156 (17.4%)		19 (1.6%)	17 (1.3%)		1 (0.3%)	0 (0%)	
Unknown	5 (0.5%)	0 (0%)		47 (4.1%)	73 (5.6%)		18 (6.1%)	39 (12.6%)	

Data were analyzed based on on-treatment analysis. *P* values tested the null hypothesis that there is no difference between early responders and non-early responders. Univariate statistical comparisons between the 2 groups were conducted using the Pearson χ^2 test for the binomial variables and the 2-sided *t*-test for the continuous variables. LASA scale has a maximum of 100 mm. FACT-An and FACT-F scores have a maximum of 52 and 80 points, respectively. Abbreviations: CLL, chronic lymphocytic leukemia; FACT-An, anemia subscale of the Functional Assessment of Cancer Therapy questionnaire; FACT-F, fatigue subscale of the Functional Assessment of Cancer Therapy questionnaire; LASA, Linear Analog Scale Assessment; N/A, not applicable; QOL, quality of life; QW, once-weekly dosing regimen; SD, standard deviation; TIW, 3-times weekly dosing regimen.

Results

Population Stratification: Early Hemoglobin Response

The proportions of early responders by study are presented in Figure 1. In each study, approximately 50% of patients experienced an early Hb response using the OT analytical approach. The proportions were slightly lower when the LVCF approach was used. Table 1 shows that early responders and non-early responders had some baseline characteristics that were statistically different. In our subsequent analyses, we therefore conducted both univariate and multivariate analyses. The latter attempted to isolate the effects

on the outcomes attributable to early response, after adjusting for differences in characteristics (age, gender, tumor type, baseline ECOG performance status, tumor response, and a binary variable to indicate use of platinum chemotherapy) between the 2 groups.

Comparison of Early and Non-Early Responders

Subsequent Transfusion Requirements: Among the 3 studies, the percentage of early responders receiving red blood cell transfusions between the end of week 4 and end of study varied between 5.1% and 7.7% (Figure 2). These proportions were statistically significantly lower ($P < .0001$ for the 3 studies) than those seen in the non-early responder group (20.1%–26.8%). This analysis was based on the OT analysis set of patients on study beyond week 4 (indicated by at least 1 post–week-4 Hb level reading). Multivariate analysis confirmed the findings from the above univariate analysis (Table 2). The adjusted odds ratios of transfusion between the end of week 4 and end of study for early responders relative to non-early responders were 0.25, 0.22, and 0.23 for the TIW study, QW study 1, and QW study 2, respectively ($P < .0001$ for all studies).

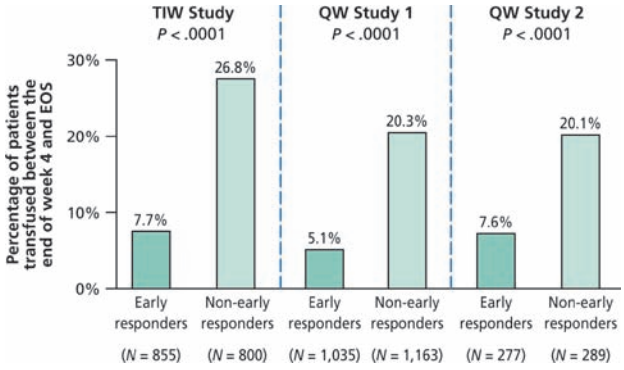


Figure 2 Proportions of patients transfused between the end of week 4 and end of study for early responders and non-early responders (univariate results). *P* value tested the equality of the proportions of patients transfused after week 4 between early responders and non-early responders. Pearson χ^2 test was used to compare the 2 groups. QW, once-weekly dosing regimen; TIW, 3-times weekly dosing regimen.

Subsequent Hemoglobin Response: Hemoglobin response rates after the end of week 4 were statistically

Table 2 Adjusted Odds Ratio of Subsequent Transfusion Requirements and Subsequent Hb Response: Effect of Early Response Relative to Non-Early Response

Outcome and Study		Multivariate Analysis	*P* value
Subsequent Transfusion Requirements			
TIW Study	No. of patients	1,654	
	Transfusion after week 4, odds ratio (95% CI)	0.25 (0.2, 0.3)	$P < .0001$
QW Study 1	No. of patients	2,178	
	Transfusion after week 4, odds ratio (95% CI)	0.22 (0.2, 0.3)	$P < .0001$
QW Study 2	No. of patients	562	
	Transfusion after week 4, odds ratio (95% CI)	0.32 (0.2, 0.6)	$P < .0001$
Subsequent Hb Response and Time to Response			
TIW Study	No. of patients	1,654	
	Hb Response after week 4, odds ratio (95% CI)	4.85 (3.9, 6.1)	$P < .0001$
	Difference in time to Hb response, days (95% CI)	–10.5 (–13.2, –7.8)	$P < .0001$
QW Study 1	No. of patients	2,178	
	Hb Response after week 4, odds ratio (95% CI)	6.25 (5.1, 7.7)	$P < .0001$
	Difference in time to Hb response, days (95% CI)	–15.0 (–17.1, –12.9)	$P < .0001$
QW Study 2	No. of patients	562	
	Hb Response after week 4, odds ratio (95% CI)	4.04 (2.7, 6.0)	$P < .0001$
	Difference in time to Hb response, days (95% CI)	–13.8 (–18.0, –9.6)	$P < .0001$

P values tested the null hypothesis that there is no difference between early responders and non-early responders. Logistic regressions were employed to report the adjusted odds ratio. Linear regressions were used to examine the association between early hemoglobin (Hb) response and the time to subsequent Hb response. Confounding factors included in the analysis were as follows: age, gender, tumor type, baseline Eastern Cooperative Oncology Group (ECOG) performance status (not available for the TIW study), tumor response, and a binary variable to indicate use of platinum chemotherapy. Abbreviations: CI, confidence interval; QW, once-weekly dosing regimen; TIW, 3-times weekly dosing regimen.

significantly higher for patients who experienced early Hb response compared with those who did not by at least 30% across the studies (Figure 3; early response of 79.8%, 84.0%, and 79.1% for TIW study, QW study 1, and QW study 2, respectively; non-early response of 43.6%, 46.5%, and 49.1% for TIW study, QW study 1, and QW study 2, respectively; $P < .0001$ for all comparisons). Multivariate analysis results show that early responders experienced statistically significantly better outcomes in Hb response and time to Hb response (Table 2). The adjusted odds ratios were 4.85, 6.25, and 4.04 for the TIW study, QW study 1, and QW study 2, respectively ($P < .0001$ for the all studies), indicating that patients with early response were 4 to 6 times more likely to experience a subsequent Hb response by the end of 16 weeks of therapy than those without. In addition, the results indicated that among patients who experienced an Hb response after week 4, those with early response experienced response on average 10.5, 15.0, and 13.8 days sooner than those without early response for TIW study, QW study 1, and QW study 2, respectively ($P < .0001$ for all studies).

Patient-Perceived Quality of Life Improvement: The improvements in QOL from baseline to week 8 or end of study were systematically greater for the early responders than non-early responders for all QOL measures, although not all QOL parameters reached a statistical significance level of $P = .05$ in the univariate analyses (Table 3). These findings were statistically significant ($P < .05$) for TIW study and QW study 1 using the 2 FACT scales, independent of the type of analytic approach used. For the LASA scores at week 8 and end of study, the mean changes over baseline were statistically higher ($P < .05$) for the early response group compared with the non-early response group in the TIW study. In QW studies 1 and 2, the improvements in LASA scores were not statistically different between the 2 groups, although patients with early response consistently experienced a greater change in LASA scores than those without. With respect to the multivariate analyses, consistent with the univariate analyses, the results show that the early response group achieved better improvement than the non-early response group. The improvement calculated from the multivariate analyses became statistically significantly different between the 2 groups across all QOL measures and studies (Table 3), with the exception of the LASA activity scale change at week 8 in QW study 2, OT analysis. The better QOL improvement seen in the early response group was robust and evident at week 8 and end of study for both OT and LVCF analyses. Although the early response group experienced greater changes in QOL than the non-early response group, the clinical sig- nificance of these results is not clear.

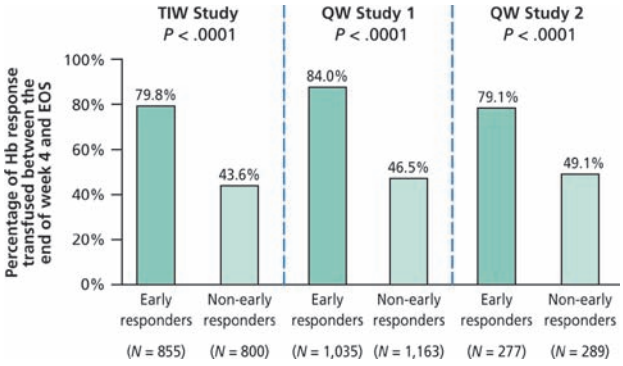


Figure 3 Proportions of patients achieving subsequent hemoglobin (Hb) response between the end of week 4 and end of study (EOS) for early responders and non-early responders (univariate results). *P* value tested the equality of the proportions of patients achieving Hb response after week 4 between early responders and non-early responders. Pearson χ^2 test was used to compare the 2 groups. Abbreviations: QW, once-weekly dosing regimen; TIW, 3-times weekly dosing regimen.

Average Weekly Epoetin Alfa Dose: The average weekly epoetin alfa doses during the 16-week treatment course for early response and non-early response groups are described in Figure 4. Patients with early response received a statistically significantly lower amount of epoetin alfa during therapy than the non-early response group ($P < .0001$ for all studies). These results indicated that patients with early response required between 16% and 25% fewer units of epoetin alfa on average during the treatment course.

Sensitivity Analysis: For the current study, early response was defined as an Hb rise of 1 g/dL or more over baseline after 4 weeks of epoetin alfa therapy, without packed red blood cell transfusions. The cutoff point of 1 g/dL was chosen to imitate the effect of 1 unit of red blood cell transfusion on patients without increased red cell destruction or sequestration.[25] Moreover, this threshold is consistent with published guidelines for determining response to epoetin alfa.[26,27] However, because Hb response varies from patient to patient, one might argue that selection of a fixed value is somewhat arbitrary. We thus conducted a separate analysis to evaluate the association of Hb rise at week 4 as a continuous variable with the previously mentioned clinical and drug utilization outcomes. The results show a statistically significant trend of

Table 3 Incremental Gain in QoL Change Scores from Baseline for Early Responders Relative to Non-Early Responders

		TIW Study		QW Study 1		QW Study 2	
		Mean (95% CI)		Mean (95% CI)		Mean (95% CI)	
QOL Measure	Analytic Approach	Univariate Analysis	Multivariate Analysis	Univariate Analysis	Multivariate Analysis	Univariate Analysis	Multivariate Analysis
Change in LASA Overall from Baseline to							
Week 8	OT	3.8* (1.1, 6.6)	5.4* (3.1, 7.8)	2.1 (–0.5 , 4.6)	3.9* (1.8, 6.0)	1.9 (–3.5, 7.3)	4.5* (0.4, 8.7)
	LVCF	4.0* (1.9, 6.1)	5.7* (3.8, 7.5)	1.9* (0.1, 3.6)	3.7* (2.1, 5.2)	2.0 (–1.9, 6.0)	4.4* (1.1, 7.8)
EOS	OT	3.7* (0.8, 6.5)	4.4* (2.1, 6.7)	1.8 (–0.8, 4.4)	4.1* (2.0, 6.3)	3.3 (–2.2, 8.7)	5.6* (1.2, 10.0)
	LVCF	4.0* (1.7, 6.2)	4.1* (2.2, 6.0)	2.0* (0.0, 4.1)	4.1* (2.4, 5.9)	3.5 (–0.9, 8.0)	6.6* (2.7, 10.4)
Change in LASA Energy from Baseline to							
Week 8	OT	5.3* (2.7, 8.0)	6.6* (4.3, 9.0)	1.9 (-0.5, 4.3)	4.1* (2.1, 6.2)	1.0 (–3.7, 5.7)	4.1* (0.1, 8.0)
	LVCF	5.2* (3.2, 7.2)	6.7* (4.9, 8.5)	1.7* (0.1, 3.4)	3.5* (2.0, 5.0)	1.2 (–2.2, 4.6)	3.8* (0.7, 6.9)
EOS	OT	5.7* (2.9, 8.5)	6.4* (4.1, 8.7)	1.8 (-0.6, 4.3)	4.6* (2.4, 6.7)	1.7 (–3.2, 6.7)	5.3* (1.0, 9.6)
	LVCF	5.7* (3.5, 7.9)	5.6* (3.7, 7.5)	2.2* (0.3, 4.1)	4.5* (2.8, 6.2)	2.4 (–1.6, 6.5)	6.1* (2.4, 9.8)
Change in LASA Activity from Baseline to							
Week 8	OT	4.8* (2.1, 7.6)	6.8* (4.4, 9.2)	1.6 (–1.0, 4.1)	4.0* (1.8, 6.2)	1.8 (–3.2, 6.8)	3.7 (–0.5, 7.9)
	LVCF	4.8* (2.7, 6.9)	6.6* (4.7, 8.5)	1.5 (–0.2, 3.3)	3.8* (2.2, 5.4)	2.0 (–1.7, 5.6)	3.5* (0.2, 6.7)
EOS	OT	5.2* (2.3, 8.1)	6.3* (3.9, 8.7)	1.2 (-1.4 , 3.9)	4.1* (1.9, 6.3)	4.5 (–0.9, 9.9)	6.8* (2.1, 11.4)
	LVCF	5.3* (3.0, 7.6)	5.3* (3.3, 7.2)	1.7 (–0.3, 3.7)	4.1* (2.3, 6.0)	4.6* (0.2, 9.1)	7.0* (3.1, 11.0)
Change in FACT-Anemia from Baseline to							
Week 8	OT	3.7* (2.1, 5.2)	4.5* (3.1, 5.9)	1.5* (0.1, 2.8)	2.5* (1.3, 3.7)	N/A	N/A
	LVCF	3.2* (2.1, 4.4)	4.1* (3.0, 5.2)	1.3* (0.3, 2.2)	2.3* (1.4, 3.1)	N/A	N/A
EOS	OT	3.3* (1.7, 5.0)	3.7* (2.3, 5.1)	1.9* (0.5, 3.3)	3.2* (1.9, 4.4)	N/A	N/A
	LVCF	3.1* (1.8, 4.4)	2.9* (1.7, 4.0)	1.9* (0.8, 3.0)	3.0* (2.0, 4.0)	N/A	N/A
Change in FACT-Fatigue from Baseline to							
Week 8	OT	2.9* (1.7, 4.2)	3.5* (2.4, 4.7)	1.4* (0.4, 2.5)	2.2* (1.2, 3.2)	N/A	N/A
	LVCF	2.6* (1.7, 3.5)	3.2* (2.3, 4.0)	1.2* (0.4, 1.9)	2.0* (1.3, 2.7)	N/A	N/A
EOS	OT	2.8* (1.4, 4.1)	2.9* (1.8, 4.0)	1.4* (0.3, 2.6)	2.4* (1.4, 3.4)	N/A	N/A
	LVCF	2.6* (1.6, 3.6)	2.3* (1.4, 3.2)	1.4* (0.6, 2.3)	2.3* (1.6, 3.1)	N/A	N/A

*Indicates that the mean change in QOL is statistically significantly higher for early responders compared with non-early responders at $P < .05$.

Univariate statistical comparisons between the 2 groups were conducted using the 2-sided *t*-test. Linear regressions were used to examine the association between early Hb response and the QOL change scores. Confounding factors included in the analysis were as follows: age, gender, tumor type, baseline Eastern Cooperative Oncology Group (ECOG) performance status (not available for the TIW study), baseline QOL score, and the change in Hb level between week 4 and week 8 or EOS. In addition to these factors, tumor response and a binary variable to indicate if the patient received platinum chemotherapy were included in the analysis of QOL change at EOS. Abbreviations: EOS, end of study; LASA, Linear Analog Scale Assessment, LVCF, last value carried forward; OT, on-treatment; QOL, quality of life; QW, once-weekly dosing regimen; TIW, 3-times weekly dosing regimen.

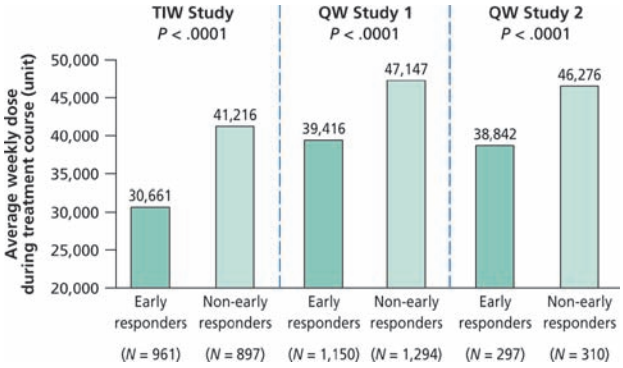


Figure 4 Average weekly epoetin alfa dose administrated during treatment course for early responders and non-early responders (univariate results). *P* value tested the equality of average weekly dose administrated during study between early responders and non-early responders. Two-sided *t*-test was used to compare the 2 groups.

decreasing transfusion requirements, increasing subsequent Hb response, decreasing time to Hb response, increasing QOL change, and decreasing drug utilization with increasing Hb change at week 4 across all studies (data not shown; all $P < .0001$), reaffirming the positive association between early Hb response and the outcomes examined.

Conclusions

Although previous studies have recognized that timely correction of anemia is desirable,[28–30] no published research analyzed and quantified the association between the timeliness of the Hb rise and patient outcomes. The results of this analysis suggest that an early Hb response to epoetin alfa is associated with improved clinical and drug utilization outcomes, including lower transfusion requirements, a higher subsequent Hb response (defined as a rise in Hb ≥ 2 g/dL over baseline independent of transfusion), a shorter time to achieve Hb response, greater improvements in QOL, and a lower average weekly dose during treatment. The benefits of early response were seen for both TIW and QW epoetin alfa regimens. Although beyond the scope of this paper, early response may also have favorable effects on costs because of lower drug use and transfusion requirements.

One potential limitation of this analysis is that the QOL instruments were not administered at week 4 in the 3 open-label studies; therefore, association of early response and contemporaneous change in QOL could not be directly assessed. Univariate analysis of the association of early response and change in QOL at week 8 and end of study did not find a statistically significant difference between the early response and non-early response groups for all QOL measures across all studies. Two factors could explain these findings. First, the LASA and FACT scales are subjective measures that depend on individual patient perception of QOL. Different individuals can have different scores even if QOL is the same using more objective measures. As a result, standard deviations from the QOL measures used are wide, making a statistically significant difference difficult to see. Second, the lack of statistical significance may have been because of subsequent changes in Hb between week 4 and week 8. The multivariate analysis attempted to adjust for this influence by controlling for the impact of changes in Hb between weeks 4 and 8 on the change in QOL at week 8. This multivariate analysis showed statistically significant findings between the 2 groups across all QOL measures and studies. These results suggest that an early Hb response is associated with contemporaneous improvements in QOL.

Another limitation of this study is the retrospective design. Because early and non-early response groups have several statistically different baseline characteristics, inferences tying early response to improved clinical outcomes can not be made directly. We addressed this issued by designing multivariate analyses that control for baseline differences. However, it is possible that other unobserved characteristics that were not measured may also be associated with early response or with the clinical endpoints studied. Furthermore, the findings from this study were based on patients treated with epoetin alfa. Whether early response benefits patients treated with other erythropoietic agents is yet to be shown.

The differences in transfusion requirements, subsequent Hb response, and epoetin alfa use are marked between the early and non-early response groups; clinical and economic significance in these outcomes is unambiguous. Despite the statistical significance of the QOL analyses, the clinical significance in QOL differences between the groups is not as clear. Overall, the early response group experienced an incremental increase in adjusted LASA score of 3.5 to 7.0 mm and an adjusted incremental increase of 2.0 to 4.5 points in FACT scale compared with the non-early response group. Whether these differences lead to clinically observable

differences must be investigated further. Berndt et al.[31] reported that a 1-point improvement in FACT-fatigue over 2 weeks corresponds with a 1-hour gain in work productivity time, 0.7-hour reduction in caregiver time, and 1.6% improvement in overall activity.

Where applicable, 2 alternative approaches of handling missing data were used in the current analysis: LVCF imputation and no imputation using OT data. The advantages of the LVCF approach are that it allows the researcher to obtain a complete data set, is simple to implement, and reflects the latest known state of the patient. The disadvantage is that it can introduce bias if missing data are intermittent or not random. Our results are not sensitive to the imputation of missing data, indicating that the findings are robust.

All 3 trials considered in this paper have shown that approximately 50% of patients with cancer receiving epoetin alfa for the treatment of anemia experience an early Hb response, and that patients who respond early to epoetin alfa therapy have favorable outcomes in subsequent blood transfusion requirements, subsequent time to Hb response, QOL score, and epoetin alfa utilization. Because the average treatment duration for erythropoietic therapies is approximately 8 to 10 weeks,[16–19] early response allows patients to experience a higher level of clinical benefit for a longer period of time. Therefore, we believe that potential for early response should be considered a criterion for selecting an erythropoietic agent, along with cost, potential side effects, and other factors.

Although this study suggests significant benefits associated with early response, factors governing the early response must be elucidated in future research. We speculate that factors related to underlying disease, chemotherapy regimen, functional iron deficiency, baseline erythropoietin level, mutation to erythropoietin receptors, low serum transferrin receptor level, marrow disorders, and insufficient dose might play a role. A predictive factor analysis based on a large prospective trial may reveal why such a variation in early response exists among patients receiving recombinant human erythropoietin. We suggest that an accurate and reliable means of predicting early response to erythropoietic agents would benefit both health care providers and patients and provide more effective therapy.

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